

ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

VOLUME 18

(OLD SERIES, VOLUME XXIII)

January to June, 1943

Contents

NUMBER 1, JANUARY, 1943

Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention	O H ROBERTSON	1
Aviation Medicine—A Brief History The Physical Qualifications for Flying, Oxygen Want and the Use of Supplementary Oxygen	LOUIS H BAUER	15
Recent Advance in the Therapy of Gout	ELMER C BARTELS	21
A Progress Report on Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts	IRVINE H PAGE, O M HELMER, K G KOHLSTAEDT, G F KEMPF, A C CORCORAN and R D TAYLOR	29
Ileostomy for Chronic Ulcerative Colitis (End Results and Complications in 185 Cases)	J ARNOLD BARGEN, WALLACE W LINDAHL, FRANK S ASHBURN and JOHN DEJ PEMBERTON	43
Prophylactic and Therapeutic Detoxication, Guanidine, Indole and Histamine	GUSTAV J MARTIN, E H RENNEBAUM and MARVIN R THOMPSON	57
Tularemia, A Report of Four Cases with Unusual Contacts	JOSEPH H SHAFFER	72
Factors Which May Influence Senescence	NATHAN SMITH DAVIS III	81
Pertinent Problems of Geriatric Medicine	EDWARD J STIEGLITZ	89
Case Reports		
Acute Thrombocytopenic Purpura Hemorrhagica with Lymphocytosis	MORRIS TAGGER and KALMEN A KLINGHOFFER	96
Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function, Report of a Case with Remarkable Tolerance	JOSEPH B KIRSNER and WALTER LINCOLN PALMER	100
Exfoliative Dermatitis Due to Phenobarbital Report of a Case with Recovery	SHERWOOD W BAREFOOT and J LAMAR CALLAWAY	105
Postoperative Precipitation of Vitamin Deficiencies	MAX ELLENBERG, HENRY DOLGER and HERBERT POLLACK	110
Editorial		112
Reviews		116
College News Notes		117

NUMBER 2, FEBRUARY, 1943

Newer Knowledge of Epilepsy	WILLIAM G LENNOX	145	
The Fraudulent Use of Digitalis to Simulate Heart Disease	O F HEDLLY	154	
Recognition of Incipient Thromboangitis Obliterans in Young Draftees	WILLIAM E JAHSMAN, ROBERT H DURHAM and NICHOLAS P DALLIS	164	
Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin	FRANKLIN B PECK	177	
The Effectiveness of Replacement Therapy in Achlorhydria	ALFRED E KOEHLER and EMANUEL WINDSOR	182	
A Method for the Continuous Recording of Gastric pH in Situ	IV Further Evaluation of the Efficacy of Antacids in Vitro and the Human Being	N E ROSSETT and JAMES FLEXNER	193
Sulfonamide Therapy of Bacterial Endocarditis, Results in 42 Cases	W R GALBREATH and EDGAR HULL	201	
Clinical Evaluation of Cedilanid	MAURICE SOKOLOW and FRANCIS L CHAMBLAIN	204	
Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease	CHARLES KLEIN, GAMLIEL SALAND and HERMAN ZURROW	214	
Case Reports			
Calcinosis and Scleroderma with Parathyroidectomy	CHARLES S BYRON and SAUL MICHALOVITZ	225	
Cor Pulmonale with Bilateral Aneurysms of the Pulmonary Artery, Interventricular Septal Defect, Patent Ductus Arteriosus and Terminal Ayerza's Syndrome	M W JOHANNSEN and CHARLES A R CONNOR	232	
Sulfur Dioxide Chemical Pneumonia, Report of a Case with Recovery Following Accidental Explosion of a Refrigerator Unit	HAROLD L GOLDBURGH and BENJAMIN A GOULEY	237	
Subacute Bacterial Endocarditis Complicating Patent Ductus Arteriosus. Case Report with Recovery Following Sulfapyridine-Heparin Therapy	WILLIAM A WINN, CLARA L HUGHES and JEWELL M SANDERS	242	
Editorial		251	
Review		255	
Editor's News Note		257	

NUMBER 3, MARCH, 1943

A Review of the Drastic Shock Therapies in the Treatment of the Psychoses	FRANKLIN G EBAUGH	279
Tuning Fork Auscultation A Test for Abdominal Adhesions	B B VINCENT LYON	297
Allergy to Injectable Liver Extracts Clinical and Immunological Observations	SAMUEL M FEINBERG, HOWARD L ALT and RICHARD H YOUNG	311
Cardiac Problems in War Time	PAUL D WHITE	323
Myxedema Heart A Pathological and Therapeutic Study	JOHN S LADUE	332
Abdominal Pain in Pulmonary Thrombosis	WILLIAM S MIDDLETON	345
Ten Years' Experience with Thorotrast Hepatosplenography	WALLACE M. YATER and FRED O COE	350
A Recording Sphygmotonomograph A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man	KURT LANGE	367
Case Reports		
Laryngeal and Systemic Histoplasmosis (Darling)	PAUL A VAN PERNIS, MIRIAM E BENSON and PAUL H HOLINGER	384
Syphilis of the Stomach, A Case Report	WALTER LINCOLN PALMER, RUDOLF SCHINDLER, FREDERIC E TEMPLETON and ELEANOR M HUMPHREYS	393
Paroxysmal Auricular Fibrillation in Association with Hiatus Hernia, Report of a Case	WILLIAM D STUBENBORD	406
Editorial		410
Reviews		414
College News Notes		416
Minutes of the Board of Regents		433

NUMBER 4, APRIL, 1943

SYMPOSIUM ON SCIENTIFIC PROOF AND RELATIONS OF LAW AND MEDICINE

HUBERT WINSTON SMITH, *Special Editor*

Editorial Introduction	445
Preface	HUBERT WINSTON SMITH 447
Foreword	ROSCOE POUND 449
Scientific Proof and Relations of Law and Medicine	HUBERT WINSTON SMITH 450

Clinical Approach to Alleged Traumatic Disease	LEOPOLD BRAHDY and SAMUEL KAHN	491
Problems of Proof in Claims for Recovery for Dermatitis	LOUIS SCHWARTZ	500
Circulatory Deficiency in the Extremities in Relation to Medico-Legal Problems	JOHN HOMANS	518
Medical Facts That Can or Cannot Be Proved by Roentgen-Ray, Historical Review and Present Possibilities	SAMUEL W DONALDSON	535
Criminal Interrogation with the Lie Detector	LEMOYNE M SNYDER	551
Legal-Medical Aspects of Blood Tests to Determine Intoxication	MASON LADD and ROBERT B GIBSON	564
Certain Medical and Legal Phases of Eugenic Sterilization	ABRAHAM MYLROSON	580
Medical and Social Factors in Crime	A WARREN STEARNS	599
Privileged Communications Is Justice Served or Obstructed by Closing the Doctor's Mouth on the Witness Stand?	ZECHARIAH CHAFEE, JR	606
Contracts Not to Practice Medicine	EDWIN MERRICK DODD, JR	618
Tort Liability of Hospitals	AUSTIN WAKEMAN SCOTT	630
Compulsory Vaccination and Sterilization Constitutional Aspects	THOMAS RIED POWELL	637
The Doctor's Federal Taxes	ERWIN N GRISWOLD	647
Traumatic Psychoses	FRANKLIN G EBAUGH and HENRY W BROBIN	666
List of Entire Symposium Series of Law-Science Articles		697
Reviews		704
College News Notes		706

NUMBER 5, MAY, 1943

Cancer of the Stomach with Special Reference to Early Diagnosis	I W HILD and IRVING BUSCH	719
The Dawn of Psychosomatic Medicine	EDWARD A STRECKLER	736
Systemic Injury to Kidneys and Brain Following Sulfathiazole Administration High Serum Sodium and Chloride Levels and Persistent Cerebral Damage	JOHN A LUTSCHER, JR and SAM S BLACKMAN, JR	741
Leukemia: Its Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy	FRANK H BETHUNE	757
Experimental Studies on Heparin and Its Influence on Toxicity and Digitation of Potassium Polychloride Venom and Other Drugs	DAVID I. MAYER	772
	FRIED	792

Ménière's Syndrome and Migraine; Observations on a Common Causal Relationship	MILES ATKINSON	797
Arachnoiditis (Diffuse Proliferative Leptomeningitis)	ALEX BLUMSTEIN and A B BAKER	809
New Trends in the Treatment of Chronic Disease An Experience in Spa Therapy	WALTER S McCLELLAN	825
Circulatory Disturbances in Prostatic Hypertrophy	MEREDITH MALLORY, FRED MATHERS, LOUIS M ORR, II, and PALMER R KUNDERT	835
Some Probative Aspects of the Early Germanic Codes, Carolina and Bambergensis	SAMUEL POLSKY and SPENCER BERESFORD	841
Case Reports.		
Amyloidosis in Chronic Atrophic Arthritis	WALTER M SOLOMON	846
Chronic Cor Pulmonale, with Report of a Case	GEORGE W COVEY	851
Calcification of Left Ventricular Infarction Recognized During Life	MILTON C BORMAN	857
Editorial		866
Reviews		870
College News Notes		872
Minutes of the Board of Regents		889

NUMBER 6, JUNE, 1943

A Comparison of the Metabolic Effects of Isocaloric Meals of Varying Composition with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms	GEORGE W THORN, JOHN T QUINBY and MARSHALL CLINTON, JR	913
The Problems of the Internist in the Navy	R E DUNCAN	920
Medical Care of Aviation Personnel	DAVID N W GRANT	926
Peptic Ulcer in the United States Navy	VICTOR W LOGAN and PAUL W BRANSFORD	929
Military Neuropsychiatry in the Present War	E H PARSONS	935
Psychoneuroses in War Time	LLOYD H ZIEGLER	941
The Treatment of Functional Gastrointestinal Disturbances of Neuropsychiatric Origin	JOSEPH C YASKIN	949
Fever Therapy	GORDON B TAYLOR	968
The Relation of the Carrier to Epidemic Meningitis	J HOWARD MUELLER	974
Carcinoma of the Lung, A Review of 31 Proved Cases at the Philadelphia Naval Hospital	FERDINAND FETTER	978
Problems of Fluid Balance in the Traumatized Patient	JONATHAN E RHOADS	988

The Relation of the Crush Syndrome to That of Burns and Other Types of Traumatic Wounds of Human Tissues	WALTER ESTELL LEE	991
35 mm Films in Diagnosis of Chest Conditions	EDMUND C BOOTS	997
Acute Nephritis and the Effect of Sulfonamides on the Kidneys	FRANCIS D MURPHY and WILBUR D WOOD	999
Medical Aspects of High Altitude Flight	DAVID N W GRANT	1006
The Present Status of Clinical Electroencephalography	FREDERIC A GIBBS	1012
Observations on Immunity in Mumps	JOHN F ENDERS	1015
Editorial		1020
Reviews		1023
College News Notes		1025
Index		1040

ANNALS OF INTERNAL MEDICINE

VOLUME 18

JANUARY, 1943

NUMBER 1

NEWER KNOWLEDGE CONCERNING THE INCEPTION OF PNEUMONIA AND ITS BEARING ON PREVENTION *

By O H ROBERTSON, M D , *Chicago, Illinois*

DESPITE the many recent advances made in the recognition and detection of the etiological agents causing acute pneumonia, the problem of the origin of this disease is still unsolved. Evidence both clinical and experimental points to the air passages as the route of infection, but the question as to how the pathogenic microorganisms gain access to the bronchial tree and what conditions are necessary to cause pulmonary infection, remain largely unanswered. It is probably a significant fact that the bacteria causing pneumonia (chiefly pneumococci, streptococci, staphylococci) are normal inhabitants of the upper respiratory tract at one time or another. Although the most frequent incitants of typical lobar pneumonia—pneumococcus Types I and II—are not commonly found in the pharynx of healthy persons, such individuals may become carriers of these types upon exposure to cases of Type I and II pneumonia, and are particularly liable to become carriers if they are suffering from a cold at the time¹. The other 30 odd types of pneumococci are found frequently and in many instances constantly in the normal throat, as are staphylococci and to a somewhat less extent hemolytic streptococci and Pfeiffer's bacilli.

Mode of Entrance of Bacterial Incitants of Pneumonia The means by which pneumonia-inciting bacteria gain entrance to the airways of the lung would seem to be limited to inhalation of droplets and the passage of fluid down the larynx. How frequently pneumonia occurs as the result of simple inhalation of pneumococcus-containing droplets we do not know. Available evidence both clinical and experimental suggests that this is not the usual source of infection. Physicians and others attending pneumonia patients must inhale considerable numbers of air-borne pneumococci, yet, when such

*Read at the St Paul meeting of the American College of Physicians April 22, 1942
From the Department of Medicine and the Douglas Smith Foundation for Medical Research of the University of Chicago, Chicago, Illinois

The Relation of the Crush Syndrome to That of Burns and Other Types of Traumatic Wounds of Human Tissues	WALTER ESTELL LEE	991
35 mm Films in Diagnosis of Chest Conditions.	EDMUND C BOOTS	997
Acute Nephritis and the Effect of Sulfonamides on the Kidneys	FRANCIS D MURPHY and WILBUR D WOOD	999
Medical Aspects of High Altitude Flight	DAVID N W GRANT	1006
The Present Status of Clinical Electroencephalography	FREDERIC A GIBBS	1012
Observations on Immunity in Mumps	JOHN F ENDERS	1015
Editorial		1020
Reviews		1023
College News Notes		1025
Index		1040

ANNALS OF INTERNAL MEDICINE

VOLUME 18

JANUARY, 1943

NUMBER 1

NEWER KNOWLEDGE CONCERNING THE INCEPTION OF PNEUMONIA AND ITS BEARING ON PREVENTION *

By O H ROBERTSON, M D, *Chicago, Illinois*

DESPITE the many recent advances made in the recognition and detection of the etiological agents causing acute pneumonia, the problem of the origin of this disease is still unsolved. Evidence both clinical and experimental points to the air passages as the route of infection, but the question as to how the pathogenic microorganisms gain access to the bronchial tree and what conditions are necessary to cause pulmonary infection, remain largely unanswered. It is probably a significant fact that the bacteria causing pneumonia (chiefly pneumococci, streptococci, staphylococci) are normal inhabitants of the upper respiratory tract at one time or another. Although the most frequent incitants of typical lobar pneumonia—pneumococcus Types I and II—are not commonly found in the pharynx of healthy persons, such individuals may become carriers of these types upon exposure to cases of Type I and II pneumonia, and are particularly liable to become carriers if they are suffering from a cold at the time¹. The other 30 odd types of pneumococci are found frequently and in many instances constantly in the normal throat, as are staphylococci and to a somewhat less extent hemolytic streptococci and Pfeiffer's bacilli.

Mode of Entrance of Bacterial Incitants of Pneumonia The means by which pneumonia-inciting bacteria gain entrance to the airways of the lung would seem to be limited to inhalation of droplets and the passage of fluid down the larynx. How frequently pneumonia occurs as the result of simple inhalation of pneumococcus-containing droplets we do not know. Available evidence both clinical and experimental suggests that this is not the usual source of infection. Physicians and others attending pneumonia patients must inhale considerable numbers of air-borne pneumococci, yet, when such

*Read at the St. Paul meeting of the American College of Physicians April 22, 1942.
From the Department of Medicine and the Douglas Smith Foundation for Medical Research of the University of Chicago, Chicago, Illinois

individuals are in good health, contact infection is rare. Attempts to produce pulmonary infection in normal animals by exposing them to atmospheres laden with droplets of pneumococcus culture have been unsuccessful. Stillman² placed mice in a chamber into which he atomized 50 c c of a highly virulent pneumococcus culture. In spite of their exposure for an hour to such an atmosphere none of the mice became infected. We have repeated these experiments using a Graesser⁸ atomizer which dispersed the culture fluid into such fine droplets that they could penetrate to the pulmonary alveoli. Likewise, we were unable to produce pulmonary infection in the mice. Stillman was able to induce pneumonia by this means only when he employed mice that had been partially immunized to pneumococcus and intoxicated with alcohol before exposure to the air-borne microorganisms. However, there is evidence that pneumonia in man may be caused by inhalation of infected droplets. One such instance occurred in our laboratory. An assistant who was apparently in good health contracted lobar pneumonia on two separate occasions within 30 to 36 hours after accidental exposure to droplets of first Type I and then Type II pneumococci.⁵

It seems more likely, as I shall attempt to indicate, that the bacterial incitants of pneumonia are usually carried into the lungs by means of infected fluid exudate from the upper respiratory tract. Before presenting evidence for this view I would like to discuss briefly the various means by which the body protects itself against the entrance of foreign material into the lung and the mechanisms employed to eliminate such noxious matter which has penetrated the lower respiratory tract.^{*} Much of the particulate material in the inspired air adheres to the mucus layer on the walls of the passages of the upper respiratory tract. Further deposition takes place on the walls of the bronchi. This mechanism of air clearing is so effective, especially in the case of dry particles, that relatively few of them reach the alveoli. It is only when dusts, carbon, silica particles, and similar materials are breathed over long periods of time in high concentration that they are found in any quantity in the air sacs. Small fluid droplets on the other hand apparently possess a much greater capacity to penetrate to the depths of the lung. Stillman and Branch⁴ exposed rabbits and mice to atmospheres containing droplets of streptococci, pneumococci and staphylococci, and were able to recover these microorganisms from the periphery of the animals' lungs. Likewise, Hamburger and the author⁷ recovered pneumococci from the peripheral lung tissue of dogs within five minutes after subjecting them to an intrabronchial spray of pneumococcus culture.

The principal mechanism for the expulsion of foreign matter from the lung is that of ciliary action which is capable of sweeping along particles at a surprising rate, 0.25 to 1 cm per minute in the bronchi and up to 3 cm in the trachea.⁶ The effectiveness of the cilia is dependent upon an intact mucus layer as shown by Proetz.⁶ When this layer is broken by drying or chemical

^{*} This subject has been dealt with at length by the author in a recent review of the literature (Proc. of Roy. Soc., 1941, xxi, 112).

action ciliary movement ceases. The narrowing and widening of the diameter of the bronchi with each respiration, the possible peristaltic movements of the bronchi, and cough all aid in the eliminatory process by way of the trachea. However, when extraneous material enters the terminal units of the airways, the alveoli, it is disposed of much less easily since the alveoli contain no cilia or musculature. The chief means employed by the body for the immobilization and removal of foreign matter in this locus is that of phagocytosis by certain large ameboid cells, the alveolar phagocytes or "dust cells" of Von Inns, normally present in small numbers in the alveolar spaces and mobilizable in large numbers in response to certain types of stimulation. Under ordinary conditions these several clearing mechanisms are so effective in the removal of particulate matter that the lungs of normal human beings are for the most part kept sterile.

Barrier of the Epiglottis Fluid entering the lower respiratory tract is distributed in a manner quite different from that of air-borne material. Liquids passing the barrier of the epiglottis tend to flow directly to the terminal parts of the lung, depending upon the viscosity of the fluid and the position of the body, and are expelled much less easily than particulate matter. The fact that the epiglottis constitutes by no means a perfect barrier to the passage of material from the upper to the lower respiratory tracts has been appreciated only in recent years. Clinicians have long felt that the pathological condition of bronchiectasis was due principally to the implantation within the bronchi of infected exudate from locally diseased areas in the nose and throat. But it was not until the relationship between lipoid pneumonia and oily nose drops was recognized by Laughlin in 1925¹⁰ that this subject received special investigation. The experiments of Walsh and Cannon¹¹ demonstrated clearly that liquids dropped into the nasal passages of animals quickly found their way into the depths of the lungs and if irritating in nature, produced an inflammatory reaction in the alveoli and lung parenchyma. Webster and Clow¹² were able to produce pneumonia in mice by the nasal instillation of pneumococcus culture.

Conditions which cause failure of the epiglottis to close completely are not well understood, but an important contribution to our knowledge has recently been made by Nungester and Klepser¹³. These workers, by means of an ingenious technic, measured the closure of the epiglottis in rats and found that lowering the surface temperature of the animal resulted in incomplete closure. Under such conditions they found that India ink, mixed with a moderately viscous mucin preparation and placed in the nares, found its way into the lungs in considerable quantities in more than half of the test (chilled) animals, whereas in the normal non-chilled controls very little or no ink was detected. Using the same technic they were able to induce pneumonia in chilled rats by the nasal instillation of pneumococci suspended in mucin in 42 per cent of the rats, whereas infection occurred in only 13 per cent of the non-chilled controls similarly injected. Like results were obtained by anesthetization with alcohol or ether.

INVESTIGATION OF CONDITIONS FAVORING THE INCEPTION OF EXPERIMENTAL PNEUMONIA

With these preliminary data before you I wish to proceed now to a brief account of an investigation which my associates and I have been conducting with the intent of determining some of the conditions within the lung which favor the inception of pneumococcus pneumonia. Although it is not unlikely that changes, both general and local, play a rôle as so-called predisposing factors, such experimental and clinical observations as are available suggest that local changes are the more important of the two. Since our study has dealt with experimental pneumonia in the dog, it will be necessary first to describe the chief characteristics of this canine disease which simulates closely clinical lobar pneumonia. Making use of such knowledge as was available concerning the inception of lobar pneumonia, namely, that it is primarily a localized infection presumably produced by pneumococci implanted in the terminal airways, and that certain conditions such as chilling acted as predisposing factors, we were able to produce pneumonia in dogs by means of injecting pneumococci suspended in a viscous starch medium into a terminal bronchus. The animals had been given a dose of morphine beforehand sufficient to lower the body temperature three to five degrees. After six to 12 hours there was a marked rise in temperature and blood count, and later, signs of consolidation both by roentgenogram and physical examination appeared. The temperature elevation was sustained three to five days, then dropped abruptly with the onset of recovery. The lesion remained localized to the infected lobe in many instances, but not infrequently spread to other lobes¹⁴. The occurrence of bacteremia, the degree of pulmonary involvement, and the outcome were found to depend largely on the size of the infecting dose. The prognostic significance of bacteremia, changes in the white count and extent of pulmonary involvement, were the same as in clinical pneumonia¹⁵. The gross pathological and microscopical examination of the lesions exhibited a striking resemblance to those of human lobar pneumonia in all stages of the disease¹⁶.

Although we were able to produce experimental pneumonia regularly by this means even with minute doses of pneumococcus culture, the procedure is a highly artificial one and left open the question as to what relationship this might bear to the problem of the inception of pneumonia in the human being. We felt that the problem could be approached most profitably by way of a study of the origin of secondary lesions occurring spontaneously during the course of experimental canine pneumonia, since it seemed possible that the local conditions responsible for a new lobar lesion might be of the same general nature as those concerned in the initiation of the primary infection.

Mechanism of Interlobar Spread Little is known of the mechanism by which interlobar spread takes place, either in human lobar pneumonia or in the experimental disease in the dog. The view generally held and an eminently reasonable one, is that new lesions arise as a result of the aspiration of

infected exudate or sputum from the primary lesion, but this conception fails to account for the manner in which the tenacious viscid material reaches the smaller bronchi of another lobe and initiates infection. In our study of the evolution of the lesion of experimental pneumococcus pneumonia in the dog, the margin of the growing lesion from a very early stage was observed to consist of edema-filled alveoli containing pneumococci (figure 1)¹⁷ A

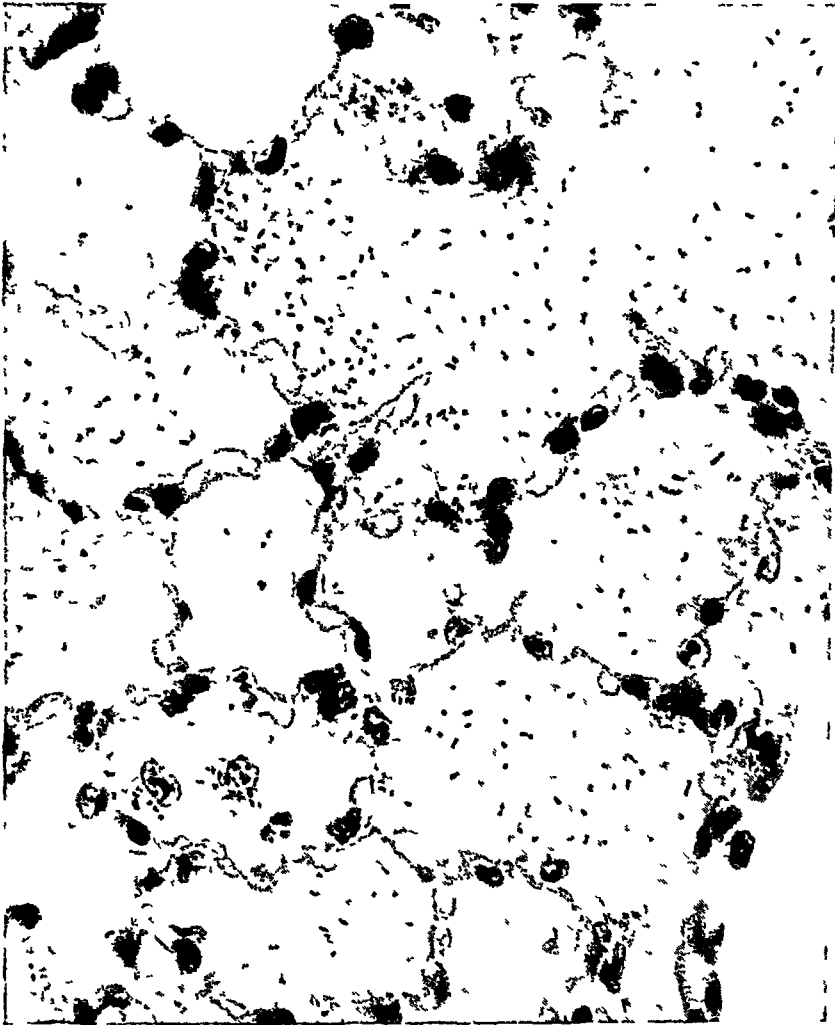


FIG 1 Photomicrograph of pneumococcus—containing edema fluid present at the margin of spreading lesions and also found here and there in the terminal air-ways of uninvolved lobes of dogs showing metastatic lesions elsewhere in the lung

similar picture is exhibited by the younger spreading lesions in the lungs of patients dying of lobar pneumonia. The amount of edema in the experimental lesion was found to depend largely on the size of the infecting dose. Lesions produced by doses of culture which result in a high mortality are much more edematous than those produced by smaller inocula from which the animals usually recover. Not infrequently the bronchi of such wet lobes,

when observed through the bronchoscope, are seen to be filled with foamy edema fluid. In this respect the amount of edema in the initial lesion is related to the incidence of spread, since metastatic lesions occur much more frequently in animals infected with the larger dosage.

In support of the concept that edema fluid may play the principal rôle in the transport of pneumococci from one lobe to another by way of the air passages, is the observed sequence of interlobar spread in canine pneumonia as related to the anatomical arrangement of the bronchi and the prone position of the dog. The relative positions of the main stem bronchi are shown in the accompanying photograph of a Wood's metal cast of the dog's

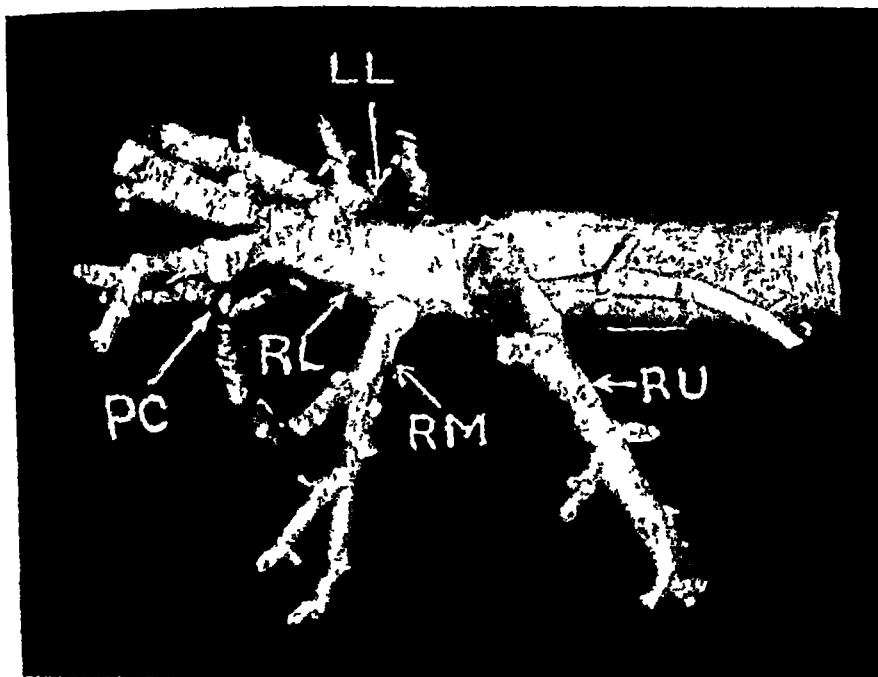


FIG. 2 Wood's metal cast of the bronchial tree of the dog as seen from the right side with the animal in the standing position. The different lobes of the dog's lung are indicated as follows: RU = right upper, RM = right middle, RL = right lower, LL = left lower, PC = post cardiac. For the purpose of clearer representation the left upper lobe bronchus has been deleted from the photograph.

bronchial tree (figure 2). The direction of interlobar spread in the dog is fairly regular. When infection is initiated in the right lower lobe with a dose which ordinarily leads to multilobar lesions, the right middle lobe, whose bronchus opens into the floor of the right main stem, is the second to become involved. Next in order of involvement are the right upper and postcardiac lobes, the respective bronchi of which leave the lateral walls of the right main bronchus and the right lower lobe bronchus. The two lower lobe bronchi are inclined at a slightly upward, i.e., dorsal angle.

With the initial lesion in the left lower lobe, the second lobe most often involved is the left upper. The bronchus to this lobe opens into the floor on the lateral side of the left main stem. When spread to the opposite side

occurs, it is almost always in the upper or middle lobes. The opposite lower lobe is with a rare exception the last to become involved.

Thus the anatomical arrangement of the bronchi, together with the fact that the dog with pneumonia lies in his cage most of the time with the head and upper thorax at a somewhat lower level than the rest of the body, affords easy opportunity for pneumococcus laden edema fluid to flow into the middle or upper lobes. However, we do not know to what extent such intra-bronchial flow of infected exudate actually occurs. Is this material continually penetrating to the depths of the uninvolved lobes in all cases of pneumonia to a greater or lesser degree? In animals with non-spreading lesions is it quickly eliminated, or in such instances does the exudate (probably small in amount) fail to reach the terminal airways?

In order to ascertain the distribution of pneumococci in the lungs of dogs with non-spreading and spreading lesions, multiple cultures were made of the peripheral areas of all the lobes of the lungs, both normal and obviously involved. Briefly, it was found that in dogs with single lobe lesions, pneumococci were recovered from the lesion itself but not from any other part of the peripheral lung tissue, whereas in animals showing spread to other lobes, microorganisms were found to be distributed widely throughout the lung in both normal appearing and consolidated lobes. Some of the microscopic sections of the uninvolved parts of the lungs of dogs with metastatic lesions elsewhere revealed small masses of pneumococcus-containing exudate in the smaller bronchi and terminal airways of otherwise normal tissue. This finding would seem to provide direct evidence for the manner in which pneumococci are transferred from the initial lesion to other lobes and highly presumptive evidence for the mode of origin of the secondary lesions.¹⁸

Artificial Production of Secondary Pneumonic Lesions If this were the correct interpretation of the mechanism of interlobar spread it should be possible to induce secondary lesions by the intrabronchial implantation of fluid pneumonic exudate in dogs with primary lesions which ordinarily are not followed by extension to other lobes. Furthermore, it should be possible to predict the lobar distribution of such secondary lesions by arranging the position of the animals so that the injected fluid would be carried by gravity into the most dependent bronchial opening nearest the point at which the exudate was deposited.

To carry out experiments of this kind fluid exudate was aspirated from the lesions of dogs infected with large doses of pneumococcus culture, both from the living animal and from the excised lungs of such dogs. The exudate which contained large numbers of pneumococci was injected by means of a rigid, small bore metal catheter inserted through a bronchoscope. An example of the result of such deposition of infected pneumonic exudate in the trachea or bronchi is shown in figure 3. This animal, infected with 0.00001 c.c. of pneumococcus Type I culture in the right lower lobe, exhibited at the end of 24 hours consolidation of the entire lobe. By 48 hours, roentgen-ray showed no further extension of the pathological process. With

the intent of producing a secondary lesion in the left upper lobe, the animal was placed on its left side with the head elevated approximately 20° and 0.25 c c pneumonic exudate injected into the trachea about three inches above the carina. This position was maintained for 40 minutes. That the exudate flowed into the infected bronchial opening was revealed by the roentgenogram made on the following day. Autopsy showed consolidation of most of the left upper lobe, as indicated in the diagrammatic representation of the excised lung.

In this way secondary lesions were artificially induced in various lobes of the dog's lung by placing the animal in an appropriate position. Likewise, it was found possible to produce lobar pneumonia regularly in normal dogs by the same technic.

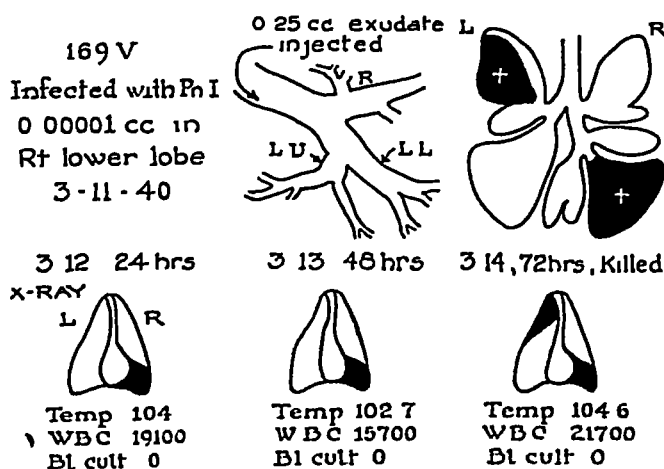


FIG 3 Production of a secondary lesion of the left upper lobe in a dog with a 48-hour primary lesion in the right lower lobe. The black areas in the diagrams of the roentgen-rays and the postmortem lungs represent consolidation. The plus sign indicates positive cultures of pneumococcus.

Control experiments on the fluidity of the exudate revealed the fact that if a viscous exudate were injected either intrabronchially or intratracheally, secondary lesions did not result. Furthermore, if the position of the animal at the time of the intratracheal injection of even a very fluid exudate was such as to favor flow away from the bronchial openings, no lesions occurred.¹⁹ The infectious material was presumably eliminated through the epiglottis.

The question arises as to what relationship these findings in the canine disease bear to the problem of interlobar spread in the human being. As indicated at the beginning of this discussion, the developing lesions of clinical lobar pneumonia exhibit the same peripheral zone of infected edema fluid which characterizes the canine lesion. Possibly the best evidence that the same mechanism of interlobar spread operates in the human patient as we believe occurs in the experimental animal lies in one conspicuous difference exhibited by the two diseases in the sequence of progressive lobar involvement. Whereas spread to the opposite lower lobe occurs commonly in human pneumonia²⁰ and constitutes by far the most frequent bilobar in-

volvement, it is rarely seen in the dog until after all the lobes on the side of the initial lesion have become involved. The semi-reclining position of the pneumonia patient would favor the gravitation of infected edema fluid into the lower lobe bronchi, whereas the prone position of the dog would have the reverse effect. Certain anatomical differences between the lungs of man and dog, aside from the position of the bronchi, make any exact comparison of the sequence of interlobar spread impossible.

EXPERIMENTAL EVIDENCE AS TO THE RELATIVE RÔLES PLAYED BY OBSTRUCTION AND IRRITATION IN THE INCEPTION OF PNEUMONIA

In addition to clarifying to a considerable degree the mechanism of the origin of new lesions during the course of pneumococcus pneumonia, the results of the foregoing experiments suggested that certain conditions are essential for the production of the pneumonic lesion: first, the implantation of pneumococci in the terminal airways, second, a fluid but viscous medium which prevents their rapid expulsion from this region of the lung, and third, the presence of local irritation such as is produced by sterile starch and also probably by the fluid pneumonic exudate which contains the edema producing substance described by Sutliff and Friedemann²¹.

In order to determine whether obstruction alone is sufficient to initiate a lesion, pneumococci were forcefully sprayed through a bronchoscope into the lower lobes of normal dogs. Following this procedure a small quantity of a viscid starch paste or mucin was injected into a terminal bronchus of one of these lobes. Pneumonia seldom resulted in these animals²². This made it seem evident that obstruction per se was not the principal factor, although we had no means of knowing whether the number of pneumococci trapped by the obstructing mass in any one locus was sufficient to initiate a lesion. Earlier observations indicated that a certain minimum number was necessary to produce infection.

Experiments were then planned with the purpose of testing the relative rôle played by local obstruction and irritation in the inception of canine pneumonia. Two parallel series of animals were injected with the same dose of pneumococci. In one series the microorganisms were suspended in an irritating, and in the other a non-irritating medium. For the non-irritating medium we made use of the device employed by Loosli²³ for the demonstration of the natural occurrence of interalveolar pores, namely, the dog's own citrated plasma which was recalcified just before injecting it into the lung. Within a minute or two after reaching the terminal airways, the plasma clotted and fixed the pneumococci in the alveoli. Five per cent starch broth paste, as ordinarily used to produce the experimental infection, was used in the other series. Sterile starch alone will produce a small localized hemorrhagic lesion. In vitro tests showed that the pneumococci grew just as well in the clotted plasma as in the starch.

It was found that all the 12 animals injected with the starch-pneumococ-

cus mixture developed pneumonia characterized by the consolidation of a whole lobe or more, whereas none of the dogs receiving the same dose of pneumococcus culture suspended in plasma became infected. When killed 24 hours after injection the lungs of these latter animals showed only small areas of atelectasis at the site of infection which were usually sterile on culture. In a second experiment of the same kind a much larger infecting dose was employed. Almost half the dogs injected with plasma in this series developed pneumonic lesions, indicating that if a sufficient number of microorganisms are trapped in the terminal airways obstruction alone may be sufficient to produce infection ²⁴

RELATIONSHIP OF EXPERIMENTAL FINDINGS TO POSSIBILITIES OF PREVENTION OF PNEUMONIA IN HUMAN BEINGS

What bearing do these experimental findings have on the occurrence of pneumonia in human beings? Since the common cold or upper respiratory infection is by far the most frequent antecedent of pneumonia, this condition should be considered first. It is well known that during the course of a cold the bacterial flora in the upper respiratory tract increases markedly ²⁵. If, in addition, the patient acquires types of pneumococci other than those he habitually carries, especially Types I and II, the chances for lower respiratory infection are increased. Then all that is needed for implantation of pneumococci or streptococci in the lung is the passage of sufficient fluid exudate past the barrier of the epiglottis. The added factor of irritation of the lower respiratory tract may be present as indicated by the finding of fine râles in the lungs in certain cases of severe colds. Although we do not know certainly how to prevent the occurrence of pneumonia following a cold, adequate care of the infection and especially an awareness of the rôle played by chilling and the danger of acquiring the more highly pathogenic types of pneumococci from other individuals during exposure to crowds, would, I believe, help in reducing the incidence of pneumonia.

Postoperative Pneumonia There is, however, another predisposing condition on which the results of the foregoing experiments have an important bearing, namely, surgical operations with general anesthesia. The occurrence of postoperative pneumonia, unhappily all too frequent, appears to be due to the aspiration of infected fluid either with or without attendant pulmonary atelectasis. The relationship of general anesthesia to incomplete closure of the epiglottis has been pointed out earlier in the experimental findings of Nungester ¹³. Just how much fluid from the upper respiratory tract reaches the bronchi probably depends to a large extent on the amount of secretion present in the pharynx. The presence of an upper respiratory tract infection at the time undoubtedly increases the possibility of implantation of infected exudate in the terminal airways. Indeed, the author has observed repeatedly the occurrence of postoperative pneumonia in patients operated upon at the time they had what was considered to be very mild upper res-

piratory infection The first consideration then is to defer operation, if possible, in any patient who shows the slightest sign of an infection in this region A second preventive measure is that of clearing out as completely as possible at the termination of the operation all secretions from the pharynx and larynx Following this, advantage should be taken of the effect of gravity in aiding elimination of foreign material from the lung Elevation of the foot of the bed for several hours postoperatively would assist the patient to get rid of such material as had been aspirated during the operation and also tend to prevent the flow of more fluid into the lung The striking effect of postural drainage in cases of lung abscess indicates how marked an influence gravity exerts in aiding expulsion of fluid material from the bronchi

The occurrence of postoperative pulmonary atelectasis always carries with it the possibility of infection since the effectiveness of the eliminatory mechanism of the atelectatic lobe is much reduced Our experiments on the inception of canine pneumonia showed that although small numbers of pneumococci obstructed in the terminal air passage failed to produce pneumonia in the absence of local irritation, pneumonia could, however, be produced under such conditions if the number of implanted microorganisms was sufficiently large It would seem not unlikely that postoperative collapse of the lung may be prevented by the same measures employed in its relief, namely, frequent changes in the posture of the patient from side to side and adequate ventilation of the lungs Whether all patients following general anesthesia should be given inhalation of 10 per cent CO_2 and 90 per cent oxygen is a matter for the surgeon to decide, since there is much difference of opinion on this point, at any rate frequent deep breathing should be encouraged in one way or another One of the most striking examples of the deleterious effects of immobilization of the patient after operation in older persons following removal of cataracts is that many ophthalmic surgeons consider their backs, the posterior portions of the functions of pulmonary elimination portions of the lungs that pneumonia is

Postinfluenzal Pneumonia A 1st influenza Whether the predisposing nature as that of the common cold is not ever, that irritation and injury of more important rôle in the inception of

Can postinfluenzal pneumonia be drugs? This question cannot be ascertaining the prophylaxis of pneumonia agents Several groups of workers experimental animals Gregg, Hammett, pyridine by mouth to dogs during the 2 pulmonary inoculation with pneumo-

varied but it was sufficient to produce an adequate concentration of sulfapyridine in the blood. All these animals developed pneumonia which at the end of 24 hours occupied a whole lobe, just as seen in the untreated dog. Their studies were not carried sufficiently far to determine whether chemotherapy begun before infection is more effective in controlling the course of experimental canine pneumonia than when such treatment is begun after the disease has been initiated.* Goldstein and Graef,²⁸ working with experimental pneumococcus pneumonia in rats, were also unable to prevent the disease by administering sulfapyridine before infection. Hochberg and co-workers²⁹ reported partial success in preventing experimental pneumococcus pneumonia in dogs by the prophylactic use of sulfapyridine, but their method of inoculation is open to the objection that it does not produce pneumonia regularly.

These results do not encourage us to believe that pneumonia in the human being can be prevented by chemotherapeutic agents. But certain practical considerations arise in relation to postinfluenzal pneumonia if and when we should have an epidemic of the 1918 type. The very low incidence of pulmonary complications in the recent influenza epidemic would certainly not justify the general use of chemotherapy in cases of influenza even though we possessed definite evidence that pneumonia could be prevented by this means, and there is no evidence that influenza itself is affected by any of the sulfonamide series. In the presence of an epidemic of severe influenza, on the other hand, the situation would be altered. Statistics of the pandemic during the previous world war showed that approximately 20 per cent of influenza patients developed secondary pneumonia of bacterial etiology. Roughly one-quarter to one-third of these pneumonias ended fatally. Hence, at least 5 per cent of persons contracting influenza died. Even under such conditions I believe the ideal procedure would be close observation of the patients and administration of chemotherapy at the first sign of pneumonic complications, since these drugs act very quickly and effectively in the early stages of pneumonia. However, under conditions of a severe epidemic adequate medical observation is difficult or impossible and it may well be considered advisable to treat all influenza patients with chemotherapy.

SUMMARY

In considering the means by which pneumococci and other bacterial incitants of pneumonia are carried into the lungs, evidence both clinical and experimental suggests that the escape of infected fluid exudate from the upper respiratory tract past the epiglottis plays a much more important rôle in the inception of pulmonary infection than does the inhalation of bacteria-

* Sulfapyridine and sulfadiazine have been found to be very effective in the treatment of experimental pneumococcus pneumonia in the dog^{26, 27}. In a further series of experiments carried out in this laboratory an unusually severe test was made by selecting for treatment only those dogs with a bacteremia of more than 1,000 colonies per c.c. of blood. Almost 50 per cent of 22 such animals recovered whereas not a single dog out of more than 100 controls showing similar degrees of bacteremia survived.

containing droplets. Experimental observations on pneumococcus pneumonia in the dog showed that not only does spread to other lobes occur as a result of the flow of infected exudate from the primary lesion by way of the bronchi, but that secondary lesions may be artificially induced by the deposition of such exudate in the trachea when the position of the animal is such that it favors flow of fluid into the bronchial openings. Furthermore, primary lesions can be initiated in normal dogs by the same procedure. Conditions necessary for the inception of infection appear to be (1) the implantation of microorganisms in the terminal air ways, (2) obstruction to their elimination, and (3) local irritation or injury. Experiments designed to compare the relative importance of obstruction and irritation indicated that local tissue irritation was the more decisive of the two factors in determining whether or not infection occurs.

The bearing of these observations on the prevention of pneumonia was discussed. Certain of the experimental findings, especially the effect of gravity on the flow of exudate in the respiratory tract, and recognition of the influence of general anesthesia on the closing of the epiglottis, seem to provide some general indications for the prevention of postoperative pneumonia. The possibility of preventing the occurrence of pneumonia by sulfonamide drugs does not seem very hopeful in view of the failure of such attempts in the experimental animal. However, under conditions of a severe epidemic of influenza of the 1918 type, such a procedure might well be considered advisable.

BIBLIOGRAPHY

- 1 SMILLIE, W G, and LEEDER, F S. Epidemiology of lobar pneumonia, *Am Jr Pub Health*, 1934, xxiv, 129-138
- 2 STILLMAN, E G. Presence of bacteria in lungs of mice following inhalation, *Jr Exper Med*, 1923, xxxviii, 117-126
- 3 GRAESER, J B, and ROWE, A H. Inhalation of epinephrine hydrochloride for relief of asthma in children, *Am Jr Dis Child*, 1936, lxi, 92-99
- 4 STILLMAN, E G, and BRANCH, A. Experimental production of pneumococcus pneumonia in mice by inhalation method, *Jr Exper Med*, 1924, xl, 733-742
- 5 ROBERTSON, O H. Instance of lobar pneumonia acquired in laboratory, *Jr Preventive Med*, 1931, v, 221-224
- 6 STILLMAN, E G. Persistence of inspired bacteria in lungs of alcoholized mice, *Jr Exper Med*, 1924, xl, 353-361
- 7 HAMBURGER, M, and ROBERTSON, O H. Unpublished experiments
- 8 FLOREY, H, CARLETON, H M, and WELLS, A Q. Mucus secretion in trachea, *Brit Jr Exper Path*, 1932, xiii, 269-284
- 9 PROETZ, A W. Nasal ciliated epithelium with special reference to infection and treatment, *Jr Laryng and Otol*, 1934, xlix, 557-569
- 10 LAUGHLIN, G F. Pneumonia following naso-pharyngeal injections of oil, *Am Jr Path*, 1925, i, 407-414
- 11 WALSH, T E, and CANNON, P R. Problem of intranasal medication, *Ann Otol, Rhin and Laryng*, 1938, xlvii, 579-607
- 12 WEBSTER, L T, and CLOW, A D. Intranasal virulence of pneumococci for mice, *Jr Exper Med*, 1933, lvi, 465-483

- 13 NUNGESTER, W J, and KLEPSEK, R G Possible mechanism of lowered resistance to pneumonia, Jr Infect Dis, 1938, lxiii, 94-102
- 14 TERRELL, E E, ROBERTSON, O H, and COGGESHALL, L T Experimental pneumococcus lobar pneumonia in dog, method of production and course of disease, Jr Clin Invest, 1933, xii, 393-432
- 15 ROBERTSON, O H, and FOX, J P Relationship of infecting dosage, leucocytic response, bacteremia, and extent of pulmonary involvement to outcome of experimental lobar pneumonia in dog, Jr Exper Med, 1939, lxix, 229-246
- 16 ROBERTSON, O H, COGGESHALL, L T, and TERRELL, E E Experimental pneumococcus lobar pneumonia in dog, pathology, Jr Clin Invest, 1933, xii, 433-466
- 17 ROBERTSON, O H, COGGESHALL, L T, and TERRELL, E E Experimental pneumococcus lobar pneumonia in dog, pathogenesis, Jr Clin Invest, 1933, xii, 467-493
- 18 HAMBURGER, M, and ROBERTSON, O H Studies on pathogenesis of experimental pneumococcus pneumonia in dog, secondary pulmonary lesions Relationship of bronchial obstruction and distribution of pneumococci to their inception, Jr Exper Med, 1940, lxxii, 261-274
- 19 ROBERTSON, O H, and HAMBURGER, M Studies on pathogenesis of experimental pneumococcus pneumonia in dog, secondary pulmonary lesions Their production by intratracheal and intrabronchial injection of fluid pneumonic exudate, Jr Exper Med, 1940, lxxii, 275-288
- 20 CECIL, R L, BALDWIN, H S, and LARSEN, N P Lobar pneumonia, clinical and bacteriologic study of 2000 typed cases, Arch Int Med, 1927, xl, 253-280
- 21 SUTLIFF, W D, and FRIEDEMANN, T E Soluble edema-producing substance from pneumococcus, Jr Immunol, 1938, xxxiv, 455-467
- 22 HAMBURGER, M, and ROBERTSON, O H Unpublished experiments
- 23 LOOSLI, C G Inter-alveolar communications in normal and in pathologic mammalian lungs, review of literature, Arch Path, 1937, xxiv, 743-776
- 24 ROBERTSON, O H, and HAMBURGER, M Unpublished experiments
- 25 WEBSTER, L T, and CLOW, A D Association of pneumococci, *Hemophilus influenzae*, and *Streptococcus hemolyticus* with coryza, pharyngitis, and sinusitis in man, Jr Exper Med, 1932, lv, 445-453
- 26 GREGG, L A, HAMBURGER, M, and LOOSLI, C G Sulfapyridine in experimental pneumococcal pneumonia in dog, Jr Clin Invest, 1940, xix, 257-265.
- 27 LOOSLI, C G, and ROBERTSON, O H Unpublished experiments
- 28 GOLDSTEIN, D H, and GRAEF, I Influence of sulfanilamide and sulfapyridine on experimental pneumococcal pneumonia in rats, Arch Path, 1940, xxx, 701-720
- 29 HOCHBERG, L A, HERSHMAN, B B, WINKELMAN, L, and RIVKIN, D Prevention of postoperative pneumococcus (Type I) pneumonia by means of prophylactic use of sulfapyridine, experimental study, Surg, Gynec and Obst, 1941, lxxiii, 40-54

AVIATION MEDICINE—A BRIEF HISTORY: THE PHYSICAL QUALIFICATIONS FOR FLYING; OXYGEN WANT AND THE USE OF SUPPLEMENTARY OXYGEN *

By LOUIS H. BAUER, M D , F A C P , *Hempstead, New York*

ONE of the newest specialties in medicine is that known as Aviation Medicine. It is a little different from other specialties in that it, to a large extent, comprises portions of other specialties all applied to aeronautics. It includes a certain amount of ophthalmology, otology, internal medicine, neuropsychiatry, psychology and a large amount of physiology. The whole purpose of the subject is largely preventive in nature. It involves the selection and care of the pilot and his protection against the physical forces acting upon him in the air, all with a view to preventing accidents from a physical cause.

Aviation Medicine had its origin in the first World War. The early experiences of the Allies indicated that the usual physical examinations were inadequate and that the stress and strain of flying were wearing pilots out at too rapid a rate. Little was understood about the effects of high altitude or long flying hours. Considerable information had been amassed by the time the United States entered the war and this country was able to profit by the experience of her allies. A research laboratory was established in 1917 and a great deal of experimental work was carried out there on problems of the eye, ear, physiology, psychology, altitude in general and oxygen supply apparatuses. A group of specialists drew up a physical examination outline based on what knowledge and experience were available at that time. Of course, many changes in the standards and methods of examination have been made in the past 25 years, but nevertheless, the sagacity of those early workers is illustrated by the fact that the basis of the present examination has very definite roots in the original one.

Following the war there was a slackening of interest and progress. Then in 1926 the Air Commerce Act was passed by Congress and civil aeronautics started on its noteworthy career. Physical standards again had to be revised, as civil flying does not call for quite the same qualifications as military flying. Interest again awakened in aviation medicine, and although progress was slow at first it developed momentum and by the time the second world war broke there was a widespread interest in it. The development of high speed flying and the invasion of extremely high altitudes brought new problems, not only of oxygen want and supply but of acceleration and deceleration and of low barometric pressure.

In the first war the problem was to find a machine that could keep up with

* Read at the St. Paul meeting of the American College of Physicians April 20, 1942

the man, but in this war it is to find a man who can keep pace with the machine

The military pilot is exposed to altitudes of 30,000 to 40,000 feet, to temperatures as low as 67° below zero, to speeds of 500 miles an hour, to intense glare, severe gales, to a constantly changing plane of equilibrium. In addition, he must operate a complicated machine requiring concentrated attention. It is obvious that the pilot is subjected to mental and physical stresses not resulting from any other occupation. Such being the case let us now consider the physical qualifications accepted, more or less universally, as requisite for piloting aircraft.

The Eye Good vision has always been considered extremely important. By good vision we mean normal vision both central and peripheral. The pilot must be able to see not only straight ahead but on all sides. It has been said that the pilot should really have eyes in the back of his head as well. Originally, normal vision without correction was considered essential and this still holds for the military pilot as he flies often in open ships where glasses are a hazard. For the commercial pilot normal vision with correction is acceptable provided he has a reasonable amount of vision without correction. For the private or sport flyer the only requirement is that his vision must correct approximately to normal. Peripheral visual fields must also be normal. Aircraft must be picked up out of the "tail of the eye" by the military pilot.

Another most important qualification is the ability to judge distance. This is necessary in landing, taking off and in flying in formation, where the tips of the wings of the planes are often only a few feet apart. It requires binocular vision. Distance cannot be accurately judged with one eye.

Normal color vision is necessary in detecting colored markings on planes, colored signal flares and lights, navigating lights and the character of the terrain. A green-brown color confusion is a not uncommon form of color blindness, and interpretation of the different shades of green and brown is of material assistance in determining the nature of the terrain.

Ocular muscle balance is tested because latent defects may become manifest or cause distress under the influence of fatigue or low oxygen.

A certain accommodative power is essential to read maps or the instrument board.

The eyes and their appendages are examined for ocular disease which is disqualifying.

The Ear, Nose, and Throat The elimination of all those with disease and obstructive conditions is necessary. Such conditions may light up into acute infections, interfere with free breathing, or by their toxic effects decrease adaptation to altitude and result in undue fatigue.

Hearing, formerly thought to be of little importance, has become of greater significance because of the increasing use of radio.

Equilibrium. This has in the past been a much discussed question. It is generally recognized now that in the pilot the most important factor in

equilibrium is vision and not the labyrinth. No matter how perfect a pilot's labyrinth, he is unable to maintain his ship on an even keel unless he can see the horizon or has learned to fly solely by instruments. Hence the Barany tests have been largely discarded and a simple test of self-balancing has been substituted. The Barany tests are useful, however, in demonstrating to a pilot the faultiness of the sensations derived from his labyrinth. In blind flying the pilot is taught to disregard his sensations and rely solely on his instruments. Equilibrium should be considered as a function of the whole proprioceptive mechanism, consisting of the eyes, ears, muscles, joints, skin, and viscera, from all of which certain sensations are derived assisting in maintaining balance, but the most important of these is vision.

General Physical Qualifications This portion of the examination is similar to any thorough physical examination and is intended to eliminate both acute and chronic disease which would interfere with the safe handling of aircraft. A careful history is obtained. A history of asthma, malaria within five years, syphilis (unless there is serological evidence of cure), and encephalitis are all disqualifying per se. A history of other serious illnesses such as pneumonia, pleurisy, tuberculosis and the rheumatic group serves to call attention to the necessity of a very careful examination of the organs involved. Any acute illness is disqualifying, pending recovery, and any chronic disease resulting or apt to result in impairment of physical efficiency or which renders the applicant subject to recurrences or which will interfere with his tolerating the extremes of altitude, cold and fatigue to which he will be exposed, is also disqualifying. Particular attention is paid to structural defects. Limitation of motion or function of any extremity or joint may interfere with the manipulation of the controls necessary for the safe operation of aircraft. Special attention is given to the cardiovascular system. Not only are organic heart and circulatory disease disqualifying but vasomotor instability and neurocirculatory asthenia are also eliminated. One of the tests used on all military and air line pilots is the Schneider Index. This is a circulatory efficiency test and it is based on the reaction of the pulse rate and systolic blood pressure to changes of posture and exercise.

Neuropsychic Examination It has been found that one of the commonest causes for grounding of pilots or for their inability to learn to fly, is a deficient neuropsychic make-up. Inability to relax, tenseness, poor emotional control are all common remarks on instructors' reports of "washed out" pilots. Hence, a very careful survey is made of the nervous system. This involves not only a neurological examination to eliminate organic neurological disease, but also a psychiatric examination, known as a personality study, which, in reality, is a survey of the entire mental life and reactions of the applicant. Effort is made to determine his past reactions to stress in the hope of assessing his probable reaction to stress in the future. It has been found that the stress and strain of flying affect the nervous system.

sooner and more severely than any other system. A sound, stable, neuropsychic makeup is essential. Aeroneurosis, which is much the same thing as neurocirculatory asthenia, is very prone to develop in those with any constitutional psychopathic inferiority.

It might seem that such a thorough examination covering the eyes, ears, nose, throat, equilibrium, general physical condition and neuropsychic makeup ought to be sufficient. Unfortunately, however, it is not. Many men selected by this type of examination never learn to fly. The reason is a lack of what has been arbitrarily termed "flying aptitude." When the examination is made by a skilled flight surgeon who has had thorough training and extended experience in aviation medicine, the percentage of those still unable to grasp flying is much less, but even then there are some. A great deal of research has been undertaken to find some means of assessing this aptitude. Up to the present moment no wholly satisfactory means has been found. Some tests which give promise are too complicated, require too expensive apparatus, or are too technical for routine use. Many workers are still delving into the problem and it is hoped that before long some satisfactory test can be unearthed which will give the solution.

One of the stresses to which any military or air line pilot is subjected is high altitude. This applies particularly to the military pilot. To understand the effects we must review a little physiology.

As we ascend from sea level there is a gradual fall in barometric pressure. The atmosphere at any level is composed of about 79 per cent nitrogen and a trifle less than 21 per cent oxygen. The oxygen pressure in the atmosphere then is 21 per cent of the barometric pressure for that level. For example, at sea level the total atmospheric pressure is 760 mm Hg. With the oxygen percentage at approximately 21, the oxygen pressure in the atmosphere is approximately 159 mm. When we breathe air into our lungs it absorbs water vapor amounting to 47 mm pressure and this must be deducted from the total atmospheric pressure. Hence, in the alveoli of the lung the total pressure is not 760, but 760-47 or 713 mm. Furthermore, the carbon dioxide pressure must be deducted and, too, the oxygen percentage becomes reduced about one-third before it reaches the alveoli, so that for all practical purposes the alveolar oxygen pressure at sea level is 14 per cent of 713 or 103 mm Hg. Even this disregards the CO_2 pressure. As we ascend, the barometric pressure falls steadily and we have a constantly falling oxygen pressure. Oxygen pressure is what keeps us all alive. If it falls below a certain level we become inefficient, then unconscious, and finally we will die. At 10,000 feet the alveolar oxygen pressure has dropped to 65 mm. At 20,000 feet it has dropped to 40 mm, and so it continues to decline the higher we go. At these higher altitudes the blood becomes insufficiently saturated with oxygen and symptoms of oxygen want appear. The oxygen want causes deeper breathing. The deep breathing upsets the chemical equilibrium of the blood by washing out carbon dioxide from the blood.

stream and an alkalosis develops. This alkalosis and lack of CO_2 then interferes with the dissociation of the oxygen from the hemoglobin in the tissues.

Aside from the deepened breathing the pulse accelerates and there are changes in the blood pressure. These changes vary. The systolic pressure may increase and the diastolic may decrease. Only one may change and either or both may suddenly break and the individual faint.

The effects on the central nervous system come on comparatively early. There is at first a stimulation, and this is followed by decreased attention and lack of coordination of the finer movements. These increase until judgment, memory and vision diminish and fainting occurs. The pilot is wholly unaware of these symptoms. Not only may he be completely inefficient but may actually lapse into unconsciousness without realizing anything is at all unusual.

Up to a certain point all symptoms may be eliminated by the use of supplementary oxygen. By increasing the percentage of oxygen in the inspired air one increases its pressure. The amount necessary to restore one to sea level condition increases gradually up to a level of about 32,000 feet. From there up 100 per cent oxygen is necessary and gradually there is again a falling available oxygen pressure and consequent inadequate saturation of hemoglobin. For example, at 44,000 feet the hemoglobin is only 65 per cent saturated. At 47,000 feet the barometric pressure has fallen to 100 mm Hg. From this must be deducted the 47 mm of water vapor pressure, leaving only 53 mm total of possible oxygen and carbon dioxide pressure, even though the individual is breathing 100 per cent oxygen. At these extreme heights nitrogen is given off into the blood stream and hence to the alveoli, still further diluting the possible oxygen available, and leaks are bound to occur around any mask. Hence, we have a person breathing pure oxygen, suffering from extreme oxygen want and if he goes above that critical level he dies from lack of oxygen saturation and from the added factor of interference with oxygen dissociation in the tissue as already mentioned. For all practical purposes one should go above 40,000 feet only in a pressure cabin or in a pressure suit, within which the atmospheric pressure is artificially kept up to a level compatible with life, and above 47,000 feet he cannot go in any other manner. All flights in both airplanes and balloons above this level have been made in pressure cabins or similar devices.

To prevent any distress or the development of undue fatigue, oxygen should be used above 10,000 feet. Above 15,000 it is necessary for efficiency. At 25,000 feet the average person will become unconscious without it, above 35,000 feet he becomes increasingly inefficient even with 100 per cent oxygen, and above 47,000 feet he will die even with 100 per cent oxygen, unless he is in a pressure cabin or suit.

There are various ways of using supplementary oxygen, but the accepted way in this country is to use gaseous oxygen with a mask preferably covering both nose and mouth. In fact, such a mask is essential in the higher alti-

not. As a rule, the air is not so pure at high altitudes as at 25,000 feet but even at 25,000 feet the air is not as pure as the oxygen. Most of the B. I. is of similar purity to the air at 25,000 feet.

At 25,000 feet the air is about 25% less dense than at sea level with the effects per cc. of O_2 being 25% greater. At the high level, nitrogen is given off in the blood, and the blood is more "free" to the lungs. The air is also "drier" as that found at sea level is "drier" at 25,000 feet, which has been shown as the "drier" the air is, the more "drier" it is. Also we have to deal with the tremendous exposure to the sun's rays at great altitudes. These matters, and the fact that the air is not well suited to life, are where

SUCCESSFUL TREATMENT OF GOUT*

By ELMER C BARTELS, M D , F A C P , *Boston, Massachusetts*

GOUT has received widespread publicity during the last 10 years, with most writers giving attention to all the various phases of the disease except the prevention of recurring attacks. We have in reality reached a point in the therapy of gout similar to that in diabetes if investigators in that field had continued to give their attention to the treatment of coma and not to its prevention. Significant is the fact that leading students of gout are at present at odds on the vital question as to whether the recurring attacks of gout can be prevented. Can the treatment be offensive or must it remain defensive? Besides the accepted fact that gout shortens life, the economic aspect indicates the dire need for some type of therapy to prevent loss of time and money (figure 1). An analysis of 14 patients who had suffered

Average duration of disease	11 years
Average loss of time from work	20 mos
Average loss in salary	\$3640
Average medical expense	\$489

FIG 1 Economic aspect of gout in 14 cases

from gout for an average of 11 years showed they lost an average of 20 months away from work, with an average salary loss of \$3640 and with medical expenses of \$489.

In the latest textbook on *Diseases of Metabolism*, edited by Duncan,¹ Bauer and Klemperer state "It is unfortunate for both the patient and physician that interval therapy in the prevention of future attacks (of gout) does not exist." They admit that a high purine diet may be harmful in some cases but that the addition or omission of purine containing foods is probably ineffective in changing the clinical course of gout. They allow small amounts of alcohol and advise against the use of cinchophen. It is their opinion that a sympathetic understanding on the part of the physician is all that can be offered since recurring seizures defy all therapeutic efforts.

Hench² does not agree with this discouraging outlook for patients with gout. He believes that by faithfully adhering to well planned interval treatment, patients can reduce the number and severity of acute attacks and thereby reduce the chance of chronic gouty arthritis and perhaps the late manifestations and complications of the disease. His plan consists of a reduced purine intake, avoidance of alcohol and the intermittent use of "urate eliminants" when necessary. These latter substances include aspirin, sodium salicylate, neocinchophen or cinchophen. This combination of diet and drugs is directed at control of the hyperuricemia.

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942

There is a noteworthy absence in the literature on gout of any statistical studies giving the results of carefully observed interval treatment. It was this fact which Bauer and his coworkers used in discounting the results of those who advocate interval treatment. They wished proof of the value of interval treatment through a carefully controlled study of a sufficient number of subjects on a constant regimen in which the level of the blood uric acid was taken into consideration. The present study meets these investigative requirements.

Basis of Present Treatment In 1935 Lockie and Hubbard³ proposed the use of a high carbohydrate, low fat diet for the treatment of gout. Their suggestion was based on the fact that a high fat diet was found to provoke attacks of gout. Earlier (1925), Lennox⁴ demonstrated that a high fat diet causes a retention of uric acid, which was confirmed by Adlersberg and Ellenberg,⁵ and Lennox suggested the use of a low fat diet in the treatment of gout.

- A Low purine intake relieves overtaxed purine metabolizing mechanism
- B High fat intake increases tubular resorption of urates
- C High carbohydrate intake produces uric acid diuresis
- D Cinchophen produces uric acid diuresis

FIG 2 Rationale of treating gout with low purine, low fat, high carbohydrate diet and cinchophen

The plan of treatment utilized in this study (figure 2) was begun at the Lahey Clinic early in 1937, a preliminary report of satisfactory results having been made in 1939⁶. It consists of a diet low in purine and fat and high in carbohydrate, to which is added the periodic administration of cinchophen. The mode of action of this regimen is multiple. Purine restriction relieves the overburdened purine metabolizing mechanism, the low fat intake prevents purine retention, and the high carbohydrate aspect of the diet tends toward the diuresis of uric acid. To the diet is added cinchophen to further uric acid elimination. The cinchophen is given at the beginning of treatment according to the plan of Graham⁷ (7½ grains three times a day for three days a week) which has been popularized by Hench. Alcohol is not permitted since most students of gout recognize it as harmful.

As treatment progresses, periodic determinations of the uric acid are made at one to three month intervals, and when a reduction in the serum uric acid occurs the dose of cinchophen is reduced from three days a week to two, to one, and omitted entirely when the uric acid reaches a normal or near normal level. Patients understand that the diet is the basis of treatment and that it is to be followed indefinitely. However, if the uric acid continues at a normal level, a more liberal diet is given.

Acute attacks of gout have been treated (figure 3) by the intravenous injections of glucose in addition to the plan outlined. Since the diet is low in both vitamins A and B, these vitamins are added. At times in gouty arthritis physiotherapy is helpful and large tophi are removed, if troublesome.

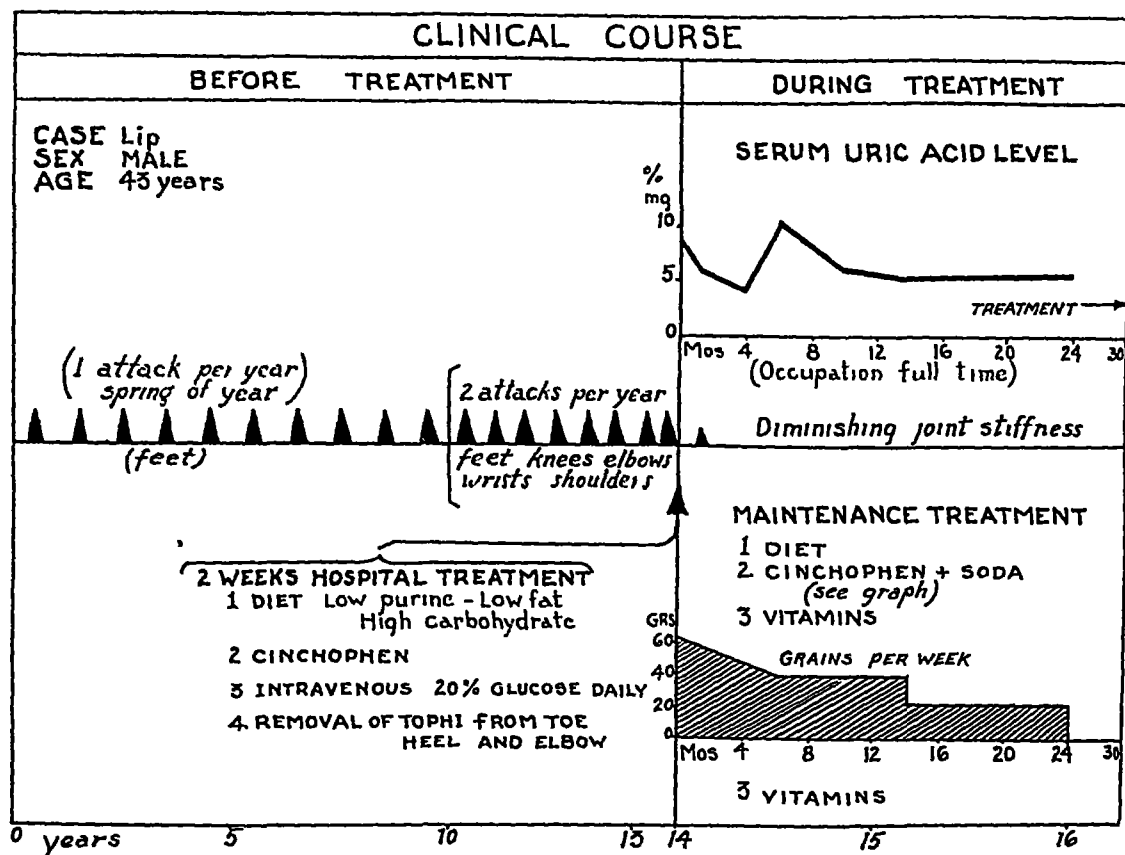


FIG 3

Patients Treated Increasing numbers of patients with gout have come under our observation (table 1), and it has been possible to follow the course of many of these patients at frequent intervals. The results of treatment of 38 patients who were carefully followed are herewith reported. All of these patients with the exception of three were seen prior to January 1941. These three were included because they had had their disease for a sufficient

TABLE I
New Cases of Gout

Year	Number of Cases
1930	2
1931	2
1932	7
1933	2
1934	11
1935	12
1936	9
1937	12
1938	14
1939	21
1940	41
1941	50
Total	183

length of time to produce a constant pattern of attacks All of these cases were followed up to January 1942

Results of Treatment These 38 cases have been divided into three groups The first group includes 18 patients who have had the disease over nine years, in all of whom a pattern of attacks had been well established (figure 4) The second group contains 13 patients who have had the disease for seven years or less (figure 5) In both of these groups the diet plan was carefully adhered to and cinchophen was used in decreasing doses In the

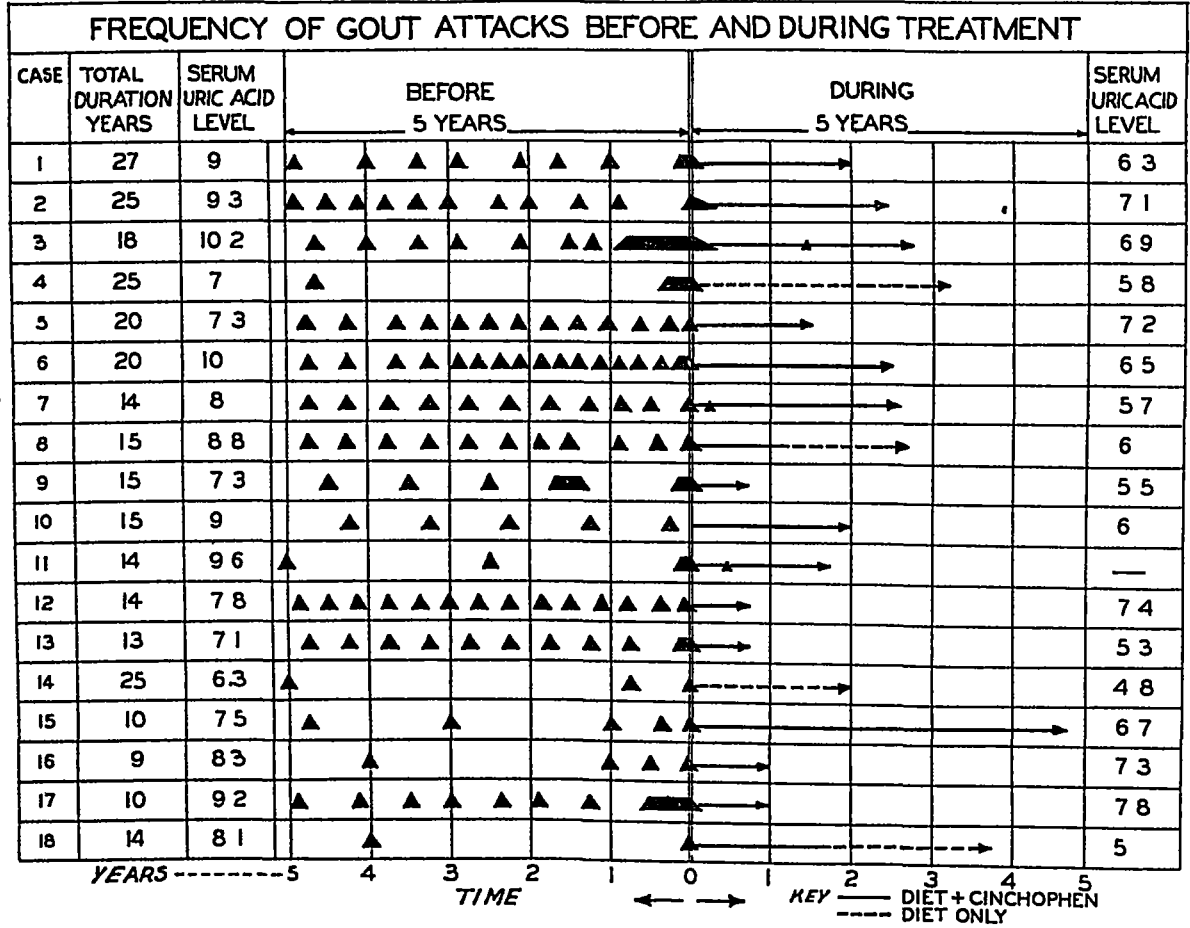


FIG 4

third group (figure 6) have been placed seven patients who had the disease from three to 15 years None of these patients followed the diet carefully, usually saying "50 per cent," and all used alcohol in varying amounts Some of these patients took cinchophen, but without regularity

The result of therapy in the first two groups was found to be satisfactory since two major requisites for successful therapy were met. (a) drop in uric acid level and (b) prevention of further attacks (figure 7) The 18 patients in the first group had suffered from attacks of gout for an average of 17 years, the longest time being 27 years The serum uric acid level when they were first seen varied from 6.3 mg per cent to 10.2 mg. per cent, the

average being 8.3 mg per cent. These patients were treated for an average of two years, during which time there were only three minor episodes in the entire group as compared with 61 major attacks during an equal time before treatment. The uric acid level fell to an average of 6.3 mg per cent. Diet

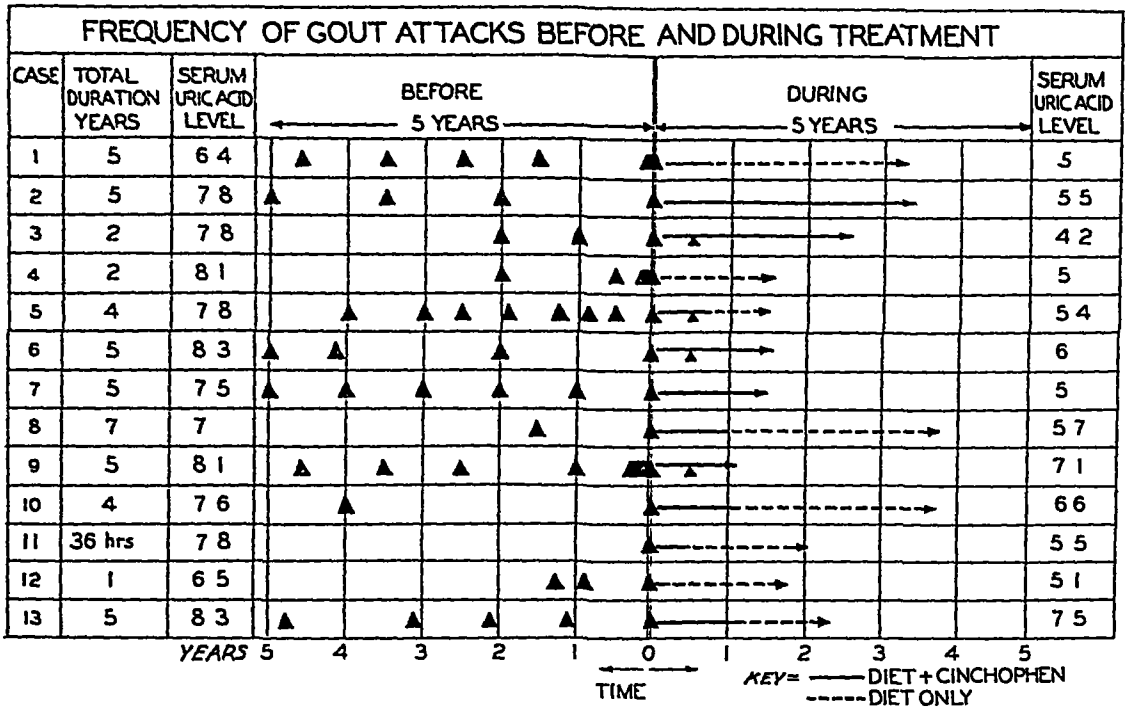


FIG 5

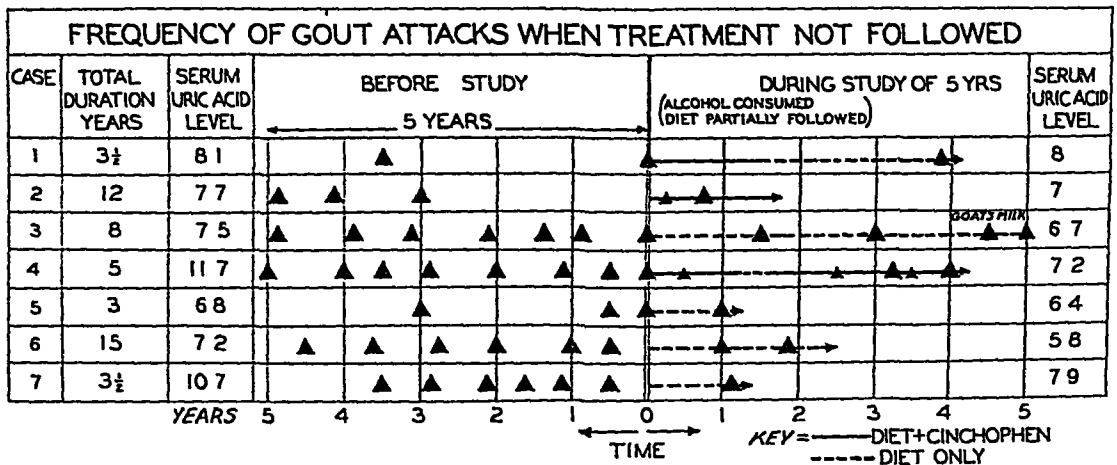


FIG 6

and cinchophen were used three-fourths of the total time the patients were treated and diet alone approximately one-fourth of the time.

The 13 patients in the second group had had attacks of gout over an average period of four years, with an average uric acid level on admission of

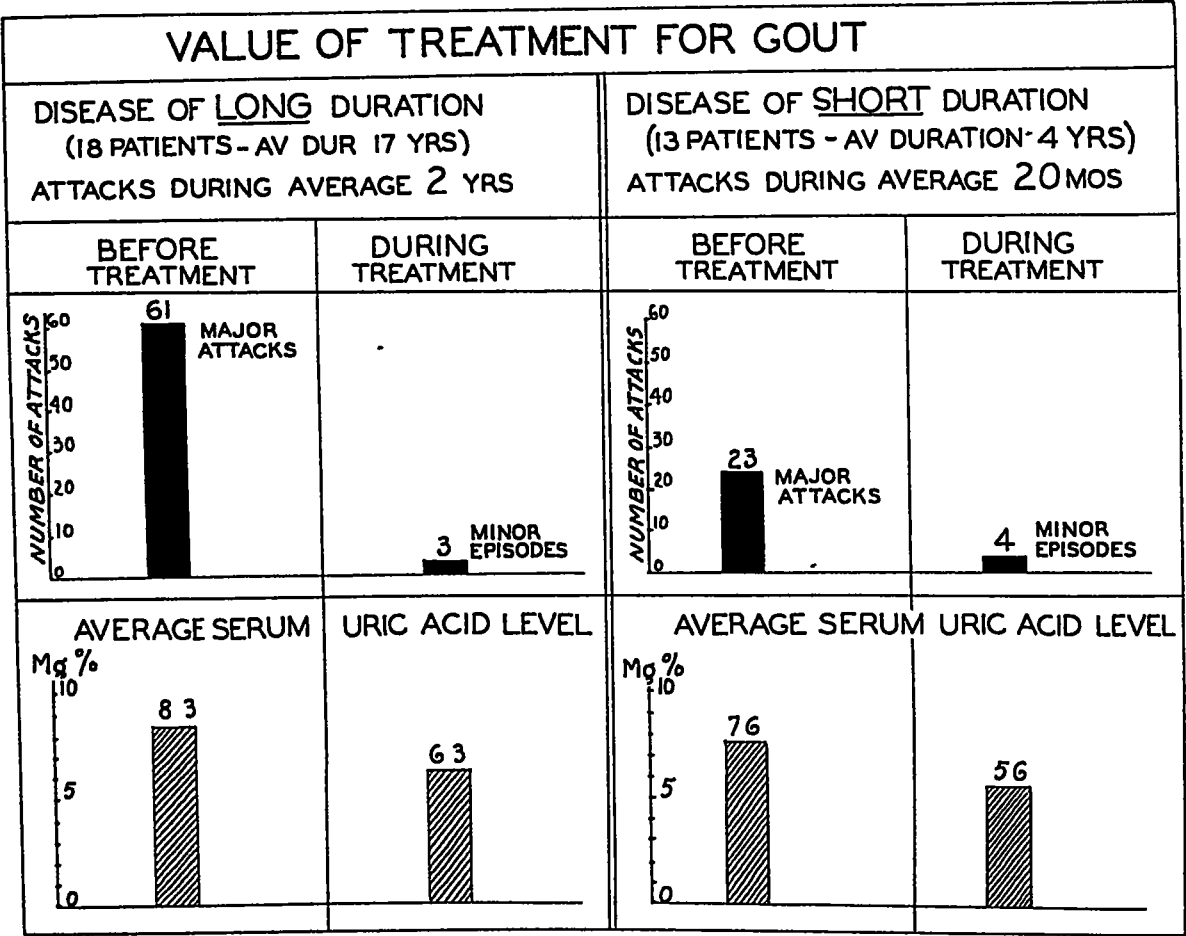


FIG 7

7.6 mg per cent In the average period of 20 months during which time these patients were treated, four minor attacks of gout occurred as compared with 23 major attacks during an equal period before treatment was begun. A combination of diet and cinchophen was used for practically the same length of time (16 patient years) as the diet alone (14 patient years).

Number of Patients	Average Duration Years	Serum Uric Acid Level Average mg %		Frequency of Attacks During Average Period of 3 Years	
		Before Treat	During Treat	Before Treat	During Treat
7	7	8.5	7	23 major attacks	12 major 4 minor attacks

FIG 8 Frequency of attacks when diet was followed only partially and alcohol was taken

The seven patients who did not carefully follow the diet (figure 8) had attacks of gout for an average of seven years, the average value of serum uric acid being 8.5 mg per cent. Over the average period of three years during which time their course was followed, 12 major and four minor

attacks took place. This number was half the number of major attacks (23) which had occurred during a similar period before treatment. The average uric acid level fell from 8.5 to 7 mg per cent.

Little difficulty was experienced in having patients adhere to the diet plan. It was necessary to make rather drastic changes in the eating habits of a number of the individuals who were accustomed to large amounts of olive oil in their food. Repeated reviews of the diet were found necessary to prevent patients from making mistakes which they honestly did not realize they were making.

It is readily appreciated that the use of cinchophen in the management of these patients permits wide criticism in the face of the inherent toxic possibility of this substance. This fear may be overemphasized as in an analysis of the toxicity of cinchophen Hench reported finding only 250 such cases in the literature, and of these, only six patients had gout. He estimated a 1 to 60,000 chance of a toxic result from the use of this drug. In our use of cinchophen any possible chance of toxicity was minimized by certain factors. (a) patients were always advised as to the early toxic mani-

TABLE II*
Serum Uric Acid Level and Non-Protein Nitrogen

Case	Serum Uric Acid Before Treatment	Serum Uric Acid During Treatment	Non-protein Nitrogen, mg %	Clinical Progress
1	6.4	6.6	44	Good
2	8.0	7.1	55	Good
3	8.3	7.3	45	Good
4	8.0	6.7	45	Good
5	6.6	7.3	40	Good
6	9.2	7.5	43	Good

festations of the drug and told to discontinue its use if such occurred. (b) It was used only as an adjunct to careful dietary management. The dose of cinchophen was reduced as the level of uric acid fell, with the patient's knowledge that its use would at some time be discontinued. (c) Since the diet was high in carbohydrate it acted to fortify the liver against toxic agents. (d) In discontinuing alcohol, possible toxicity through the synergistic or intensified action of alcohol and cinchophen on the liver was avoided. (e) A moderate serving of meat, fish or fowl was given once a day in addition to other proteins to keep the protein intake at a proper level, this being another means of fortifying the liver against toxic damage. (f) In the last two years liver function tests, by the intravenous hippuric acid method, were made at intervals during treatment with cinchophen. In some instances cinchophen was stopped because the results of the liver function test fell below normal. Since renal damage may cause faulty results in the liver function test, care must be taken in its interpretation. In the first group, 14 of the 18 patients have continued to take cinchophen at least one day a week. In the second group, those of short duration, only five of 13 patients are now taking cinchophen.

A return of the serum uric acid level to normal did not occur in all cases (nine in the first group and three in the second group) in spite of the continued use of cinchophen. This was especially true in patients in whom the disease was of long duration. It was found that this failure usually occurred in patients who had renal insufficiency, as indicated by an elevated non-protein nitrogen (table 2). These six patients responded well to treatment, as indicated by failure of recurring attacks, in spite of continued elevated level of uric acid. In four of these patients there was a decrease in the uric acid level. Perhaps continued effort to return the uric acid level to normal by the use of cinchophen need not be exerted in patients with long-standing gout or in those in whom the uric acid level has been stabilized and symptomatic benefit has been obtained.

Perhaps sufficient time has not elapsed in all the cases reported to satisfy critical evaluation of the treatment from the standpoint of preventing further attacks, since it is well recognized that at times years may separate the recurring attacks. In patients in whom this criticism may be justified, a substantial drop in the level of the serum uric acid was always obtained, which is a prerequisite to the prevention of further attacks.

SUMMARY

Indisputable benefit was obtained in a group of 31 patients with gout who carefully adhered to a low fat, low purine, high carbohydrate diet, with the addition of decreasing doses of cinchophen. On this plan of treatment seven minor attacks of gout occurred, as compared with 84 major attacks during a comparative period before treatment. This plan of treatment secured the desired results of reducing the blood uric acid level and reducing the number and severity of further attacks of gout. Even patients in the phase of chronic gouty arthritis responded to this plan of treatment. It is urged that this treatment be given further consideration by other physicians.

BIBLIOGRAPHY

- 1 BAUER, W, and KLEMPERER, F. Gout. In Diseases of metabolism, edited by G G DUNCAN, 1942, W B Saunders Company, Philadelphia, Chapter XII, pp 609-654.
- 2 HENCH, P S. Chronic arthritis, chronic infectious arthritis, chronic senescent arthritis, gout. In Modern medical therapy in general practice, 1940, Williams and Wilkins, Baltimore, pp 3298-3397.
- 3 LOCKIE, L M, and HUBBARD, R S. Gout, changes in symptoms and purine metabolism produced by high fat diets in four gouty patients, Jr Am Med Assoc, 1935, CIV, 2072.
- 4 LENNON, W G. A study of the retention of uric acid during fasting, Jr Biol Chem, 1935, LXXI, 521.
- 5 ADLERSBERG, DAVID, and ELLFANDER, MAX. Effect of carbohydrate and fat in the diet on uric acid excretion, Jr Biol Chem, 1939, CXXVIII, 379.
- 6 BARTELS, E C. The treatment of gout with a low fat, high carbohydrate diet. Preliminary report, New England Jr Med, 1939, CCXX, 583.
- 7 GRAHAM, GEORGE. The treatment of gout, Proc. Roy. Soc. Med, 1927, XX, 1.

A PROGRESS REPORT OF INVESTIGATIONS CONCERNED WITH THE EXPERIMENTAL TREATMENT OF HYPERTENSION WITH KIDNEY EXTRACTS *

By IRVINE H PAGE, M D , O M HELMER, PH D , K G KOHLSTAEDT, M D , G F KEMPF, M D , A C CORCORAN, M D , and R D TAYLOR, M D , *Indianapolis, Indiana*

At this time last year we reported to you the reasons why we believe that certain extracts of normal kidneys contain a substance, or substances, which lowers arterial blood pressure in hypertensive dogs, rats and human beings¹ It was pointed out that one of the most striking effects of these extracts was their ability to reverse the retinal arterial lesions observed during the course of the malignant phase of hypertension Their administration was also often associated with a rise in the usually depressed renal blood flow

Difficulties both in the preparation of the extract and in its use were numerous The chief among the first were (1) extremely poor yields and (2) inadequate knowledge of the chemical nature of the active substances Among the second were (1) pyrogenic reactions, and (2) occasional severe generalized reactions which appeared to be anaphylactoid in nature

We have not believed that progress in the study of this highly complex problem would be made most rapidly by neglecting further studies on the mechanism of hypertension itself For this reason investigations designed to elucidate the chemical structure of angiotonin have been actively pursued Further work on the intrarenal hemodynamic changes in the kidneys in hypertensives has shown that so-called "renal ischemia" is not necessary for the persistence of renal hypertension² Reduction of renal pulse pressure and, perhaps, moderate reduction in mean pressure seem to be adequate stimuli for its induction This suggests that anoxia of the kidneys of marked degree is unlikely, at least in the early phase of hypertension Thus, if the anaerobic decarboxylation of amino acids to form pressor amines, as suggested by the experiments of Bing,³ is a part of the mechanism contributing to the maintenance of hypertension, it would probably occur late in the course of the disease Other circumstances, as yet unknown, might, however, bring this mechanism into play during an earlier phase

Evidence is steadily increasing that angiotonin plays an important part in the regulation of the arterial blood pressure both in normal and hypertensive subjects⁴ This is of some importance because during the past year we have attempted to assay renal extracts on the basis of their ability to destroy angiotonin From this naturally springs the suggestion that the

* Read at the St Paul meeting of the American College of Physicians April 21, 1942

clinical effect of renal extracts is due to their ability to destroy circulating angiotonin. Attractive as this view may be, it remains unproved.

It is unnecessary to burden you with the story of the many failures we have had in attempts to purify kidney extract. A résumé is given of one method we are now actively investigating which may be of interest to those studying the subject themselves.

Preparation of Kidney Extract Briefly, the steps involved are (a) extraction of the ground kidney with aqueous solution of acetic acid and salt, (b) raising the temperature to 56°C , (c) precipitation with ammonium sulfate to full saturation, (d) redissolving the precipitate and addition of ammonium sulfate to 25 per cent saturation, (e) dialysis of the supernatant solution to remove the ammonium sulfate and concentration, (f) addition of 'Merthiolate' (Sodium Ethyl Mercuri Thiosalicylate, Lilly) and passing the solution through a Seitz filter. The detail is considerably modified from our original method (Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran⁵).

Ten kilos of fresh pork kidneys are ground through a fine meat chopper (Tiffany's) into 15 liters of distilled water to which 300 gm of sodium chloride and 300 cc of glacial acetic acid have been added. The vessel containing the mixture is stirred rapidly with a mechanical stirrer while the temperature is raised to 56°C . This temperature is reached in about 10 to 15 minutes and held there for 6 to 15 minutes, depending upon the appearance of a definite clumping of the inert protein.

To the clear filtrate, 632 gm of ammonium sulfate per liter are added with stirring. The mixture is allowed to stand overnight at room temperature. The precipitate is then collected on Buchner funnels, No 54 Whatman paper being used. The filtrate is discarded. The precipitate is dissolved in 2 liters of water, the ammonium sulfate content determined in an aliquot by direct nesslerization, and a total of 532 gm of ammonium sulfate per liter is added with stirring. The precipitate which forms is collected on Buchner funnels, using No 50 Whatman paper, a small amount of diatomaceous earth (hyflo-super-cel) being added to insure a clear filtrate. The filtrate is discarded. The precipitate is dissolved in 15 liters of water, the ammonium sulfate content of the solution is determined, and then a total of 190 gm per liter of ammonium sulfate (25 per cent saturated) is added with stirring. The precipitate which forms is removed by gravity filtration in the cold through No 5 Whatman paper and discarded. To the filtrate of the 25 per cent saturated precipitation 513 gm of ammonium sulfate are added with stirring. The precipitate which is formed is collected on Buchner funnels, using No 5 Whatman paper, diatomaceous earth being used as before. The precipitate is dissolved in a minimum amount of water and dialyzed overnight against running tap water (15°C or below) and then against distilled water in cellophane sacs to remove the ammonium sulfate. Any precipitate of euglobulin which forms during the dialysis is removed and the extract concentrated in vacuo so that 1 c.c. of the material is equivalent to 100 to 170 gm of original kidney.

The extract is centrifuged at high speed to remove any sediment which forms during the concentration. Sodium chloride is added to 0.8 per cent and the extract filtered through a Seitz filter. 'Merthiolate' may be added to it in a concentration of 1:5,000 after the extract is put through the Seitz filter. It is preferable to clarify the extracts before filtering through a Seitz filter by a preliminary filtration through a medium or fine Pyrex fritted filter*.

Extracts prepared in this manner lower blood pressure but are not free from pyrogens and materials which elicit shock-like reactions. Treatment of the final extract with 1 to 2 grams of kaolin per 250 grams of

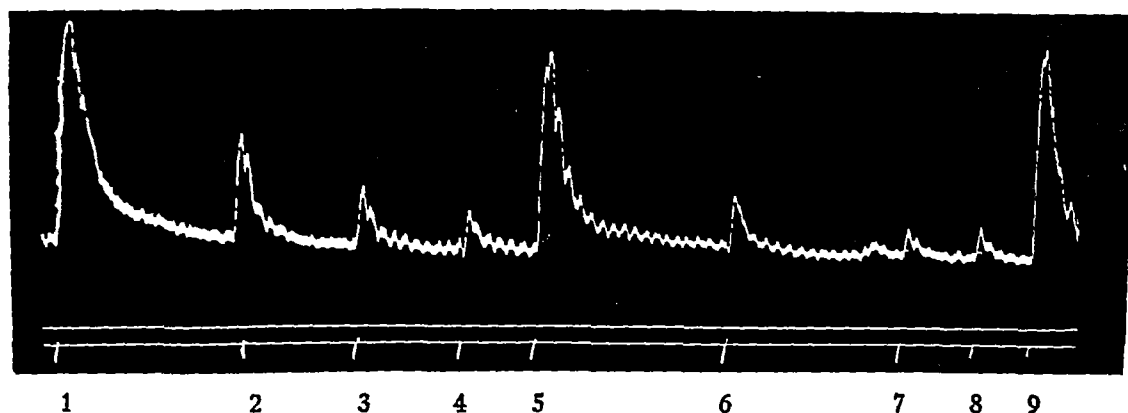


FIG 1 The *in vitro* destruction of angiotonin by renal extracts as measured by pressor response produced by intravenous injections into a pithed cat

Injection No 1 Angiotonin 0.05 c.c. as control

2, 3, 4 Injections of mixtures of a renal extract derived from 200, 400, 800 mg. of fresh kidney tissue and an equivalent amount of angiotonin, incubated for 30 minutes at 37° C and then heated to 100° C for 10 minutes

5 Angiotonin 0.05 c.c.

6 Injection of another renal extract derived from 1000 mg. of kidney and the equivalent amount of angiotonin

7, 8 Injections of a mixture of renal extract prepared from 800 mg. of kidney and the equivalent amount of angiotonin

9 Angiotonin 0.05 c.c. control

kidney at pH 4.0 while raising the temperature to 55° C removes some of this material. This may be followed by reprecipitation with ammonium sulfate to 0.6 saturation. The final extract after dialysis should always be made isotonic before injection.

Assay of Potency The assay of kidney extract in hypertensive rats and dogs is extremely time consuming and requires large amounts of material. Wide variations in response are observed in individual animals and this further complicates an already complicated problem. The need for a simpler test was apparent.

The following test must be considered as merely an experiment at the present stage (Helmer, Kohlstaedt and Page⁶). It is based on the pos-

* No 10-358 in the Fisher Scientific Company catalogue

sibility that angiotonin is the effector substance in hypertension; hence the ability of kidney extract to destroy angiotonin in vitro might be a measure of its antipressor activity

One c c of extract equivalent to 12.5 to 100 mg of original kidney is mixed with 1 c c of fiftieth molar buffer at the desired pH (4.0 or 7.0) and incubated at 37° C for 30 minutes with 0.5 c c of standardized angiotonin solution. The reaction is halted by immersion of the tube in boiling water. The pressor response of an aliquot portion of the test solution is compared to that of untreated angiotonin by intravenous injection into pithed cats.

In order to compare readily the results of the assays the following index of angiotonin-destroying power was utilized

$$\text{Angiotonin Index} = \frac{1}{\frac{\text{Pressor response in mm Hg unknown}}{\text{Pressor response in mm Hg standard}}} \times \frac{\text{mg kidney}}{100}$$

Two Enzymes (Angiotonases) with Different pH Optima in Kidney Extract Two enzymes with optimal ability to destroy angiotonin at approximately pH 4.0 and pH 7.5 respectively were found in our kidney extracts (table 1)

TABLE I
Effect of pH on Ability of Kidney Extract to Destroy Angiotonin

pH	Acid Stable Index	Alkaline Stable Index
4.0	0.69	0
5.0	0.55	0
6.0	0.50	1.38
7.0	0.34	4.00
7.5	—	5.88
8.0	0.28	2.94

We have attempted to correlate these results with those obtained from the tests on hypertensive rats. In calculating the *rat index* consideration was given to the amount of extract administered to lower the blood pressure in relation to body weight of the rat and the number of days required to lower the pressure. The index follows

$$\text{Rat Index} = \frac{1000 \times (1, 2, 3 \text{ or } 4 \text{ anti-pressor action})}{\text{gm kidney Kg body weight} \times \sqrt{\text{days treated}}}$$

Grade 1, 2, 3 and 4 results are appraised as follows. Rats with systolic blood pressure averaging 180 to 200 mm of mercury are used. Results are graded according to (1) the fall in blood pressure, (2) its duration, and (3) the presence or absence of signs of illness or reaction as evidenced by weight loss, hemorrhage, respiratory difficulty, etc. The fall and subsequent rise of pressure on discontinuing treatment must not be due to accidental occurrences such as may be associated with extremes of heat or cold nor due

to spontaneous changes in blood pressure which might occur in any one hypertensive animal

Grade 1 is equivocal and not considered significant unless all animals on test follow the same course, or unless the animal had maintained a steady pressure above 200 mm and shows a sustained fall below 170 mm

Grade 2 A fall in pressure to between 140 mm and 155 mm or a well sustained fall below 160 mm

Grade 3 A fall in pressure to from 130 to 140 mm or a well sustained fall below 150 mm

Grade 4. A fall in pressure below 130 mm sustained at least two days

The correlation between the two indices, especially when the angiotonin-destroying capacity is measured at pH 7.0, is reasonably good. It is our hope that this test in which in vitro destruction of angiotonin is employed will finally serve to replace those in which hypertensive rats and dogs are employed. Obviously, however, it must be established with certainty that angiotonin destruction and antipressor activity go hand in hand before the hypertensive animals as a test object can be abandoned. This has not as yet been accomplished.

Our animal and clinical results, however, suggest that the kidney extracts prepared to contain the enzyme with pH optimum at 7.0-7.5 is more active as an antipressor agent than the one with pH optimum at 4.0.

It must not be assumed that we necessarily consider the angiotonin destroying enzyme as identical with the antipressor substance in kidney extract. There is some evidence for this belief but it is insufficient to establish so important a point. We can only point out that we consider other possibilities as well worthy of investigation.

Antigenic and Shock-like Effects of Renal Extracts As indicated last year, the occasional and unpredictable occurrence of severe reactions in which the blood pressure fell to shock levels shortly after administration of extract prevented their use outside a hospital. Although it is true that with increasing purity of the extracts the number of these reactions has markedly decreased, the fact that they remain unpredictable in their appearance necessitates further careful analysis of this problem. It has not been solved yet, but some of the difficulties appear to be in the process of solution.

As a means of testing the antigenicity of extracts the following method has now been in use for the past six months (Kempf and Page¹). Antiserum was prepared in rabbits by injection of kidney extract which was known to produce reactions in patients. The rabbit antiserum was used to sensitize 250 to 275 gram guinea pigs by intraperitoneal injection (0.5 cc). Trial doses of kidney extract equivalent to from 5 to 10 grams of original kidney consistently killed such sensitized animals. As purification has proceeded, extracts have been prepared of which the equivalent of 40 to 60 grams of original kidney are required to kill the animal.

We have satisfied ourselves that renin purified in such a way as to be free of angiotonase is not the cause of the reactions.

CLINICAL RESULTS

1. *Effect on Arterial Blood Pressure* Despite the fact that extracts prepared in many different ways have been used in the treatment of our patients, reduction of blood pressure, especially the diastolic, has occurred in most. Some patients appear to have been resistant and showed no sig-

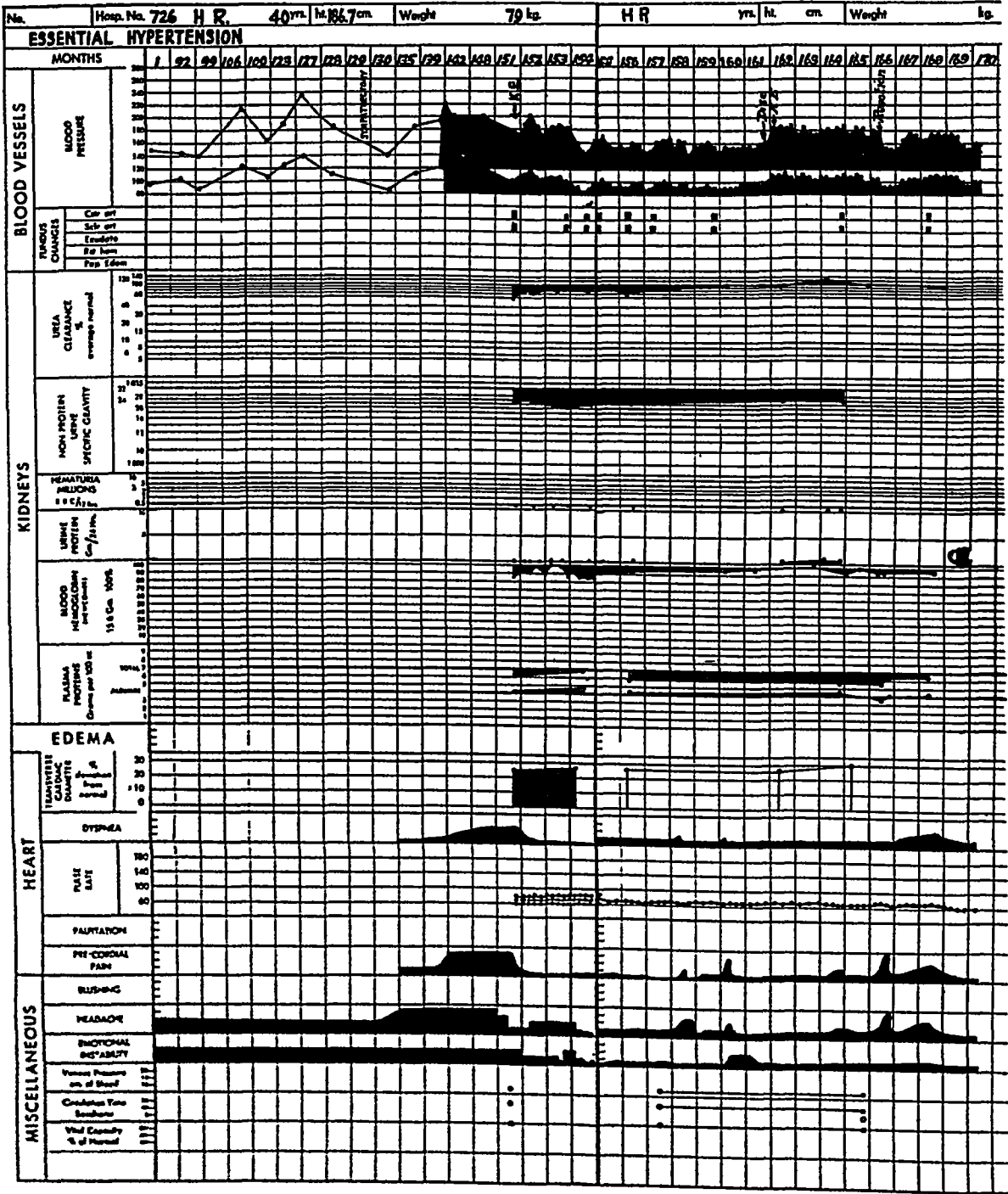


FIG 2 Example of patient with essential hypertension treated with various types of kidney extract. Each dot under "blood pressure" represents the average of 7 daily blood pressure measurements.

nificant fall This is a phenomenon we have also observed in dogs Whether it is a quantitative problem so that more extract would have lowered the pressure, we do not know

Fever as a sequel to injection of extract occurs much less frequently than during last year, and the local tissue response is also milder Indeed, in a number of patients local reactions are insignificant With reduction in the number and severity of reactions there has, however, been an associated loss of antipressor activity. In some patients it might be supposed that the entire antipressor action was due to reactions both local and general, but these seem to be the exceptions, not the rule The usual result in patients is a fall in blood pressure associated with daily febrile response of one or two degrees for the first few days of treatment After this initial period, no appreciable fever occurs Injections are given daily, and if nothing untoward happens within three weeks the patient is discharged from the hospital to our out-patient clinic for further treatment

2 *Effect on Eyegrounds* Perhaps the most impressive single change caused by administration of kidney extract is its effect in reversing the morbid changes seen in the eyegrounds of patients suffering from the malignant syndrome All patients with this syndrome, after a suitable period (usually four to eight weeks) of treatment, either were free of eyeground change or exhibited minimal signs of it It has always come as a surprise to observe diminution or disappearance of white, "hard" exudates Often they are very slow to resolve We have repeatedly observed that reversal of the eyeground changes may occur before any marked fall in blood pressure occurs Whatever its mechanism, the change is striking

3 *The Effect of Kidney Extract on Cardiac Output and Size* Contemporary evidence demonstrates that cardiac output is either normal or moderately decreased in hypertension It may be presumed that cardiac output is maintained usually at normal levels because of cardiac enlargement

Taylor and Page^{8a} have employed the ballistocardiograph to ascertain the effect on cardiac output of reducing arterial pressure by means of kidney extract In brief, it was found that in 15 patients with afebrile reduction in pressure from 174 mm Hg, mean pressure, to 140 mm Hg, cardiac output increased roughly 15 to 20 per cent When extract was discontinued and arterial pressure rose, cardiac output decreased to its former level

These results seem to be significant in the light of the fact that administration of angiotonin to normal persons leads to decrease in cardiac output and the conversion of a normal tracing to one with contours closely resembling those observed in hypertensives After treatment with kidney extract, the normal contour of the tracing reappears

It is interesting to compare the effects of other pressor agents such as tyramine and methylguanidine with angiotonin in normal human beings The most striking facts which emerged were that tyramine and methylguanidine produce very severe and disagreeable signs and symptoms and ballistocardiographic tracings with contours quite different from those of

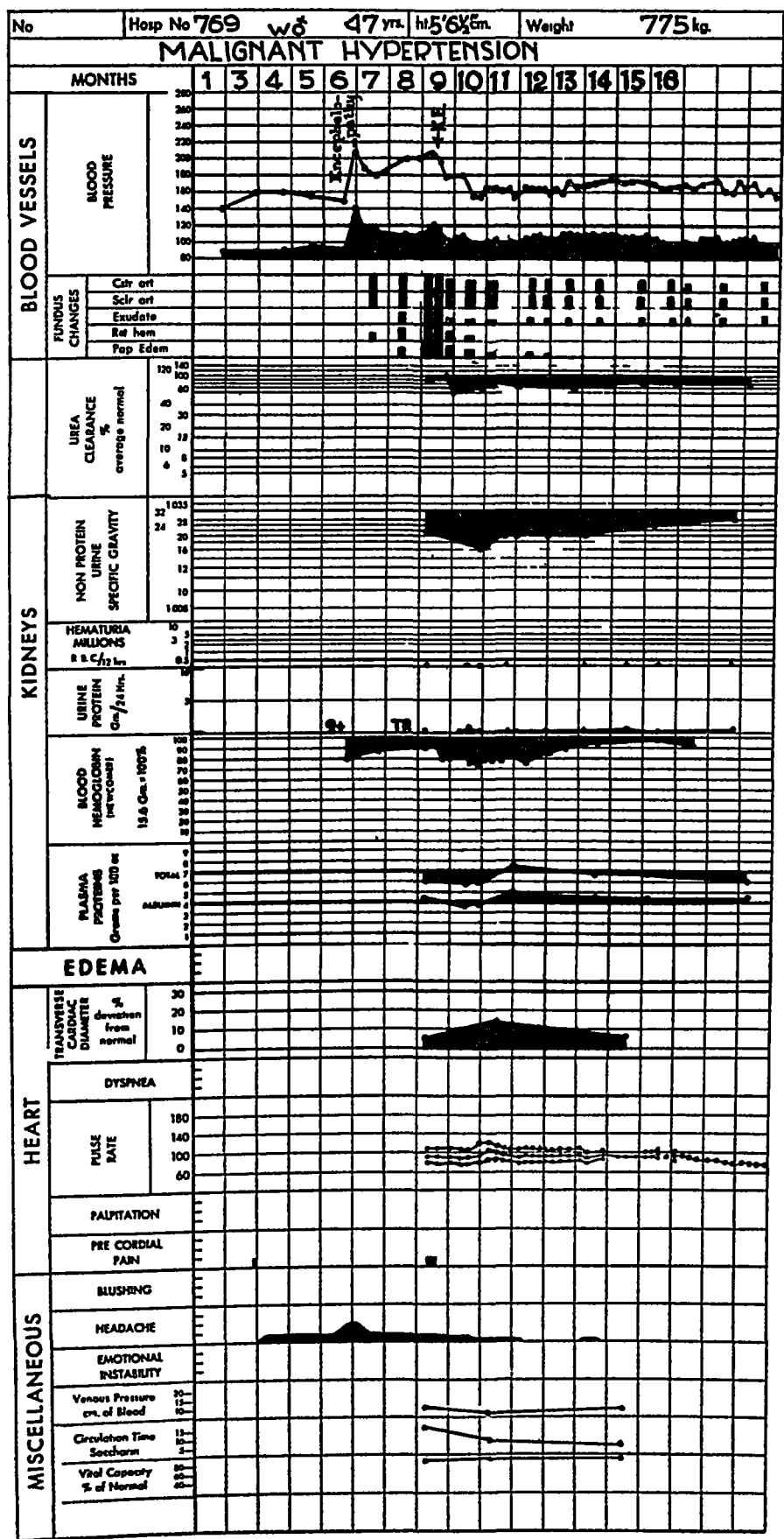


FIG 3 Example of a patient with malignant hypertension treated with extract of sheep's kidney.

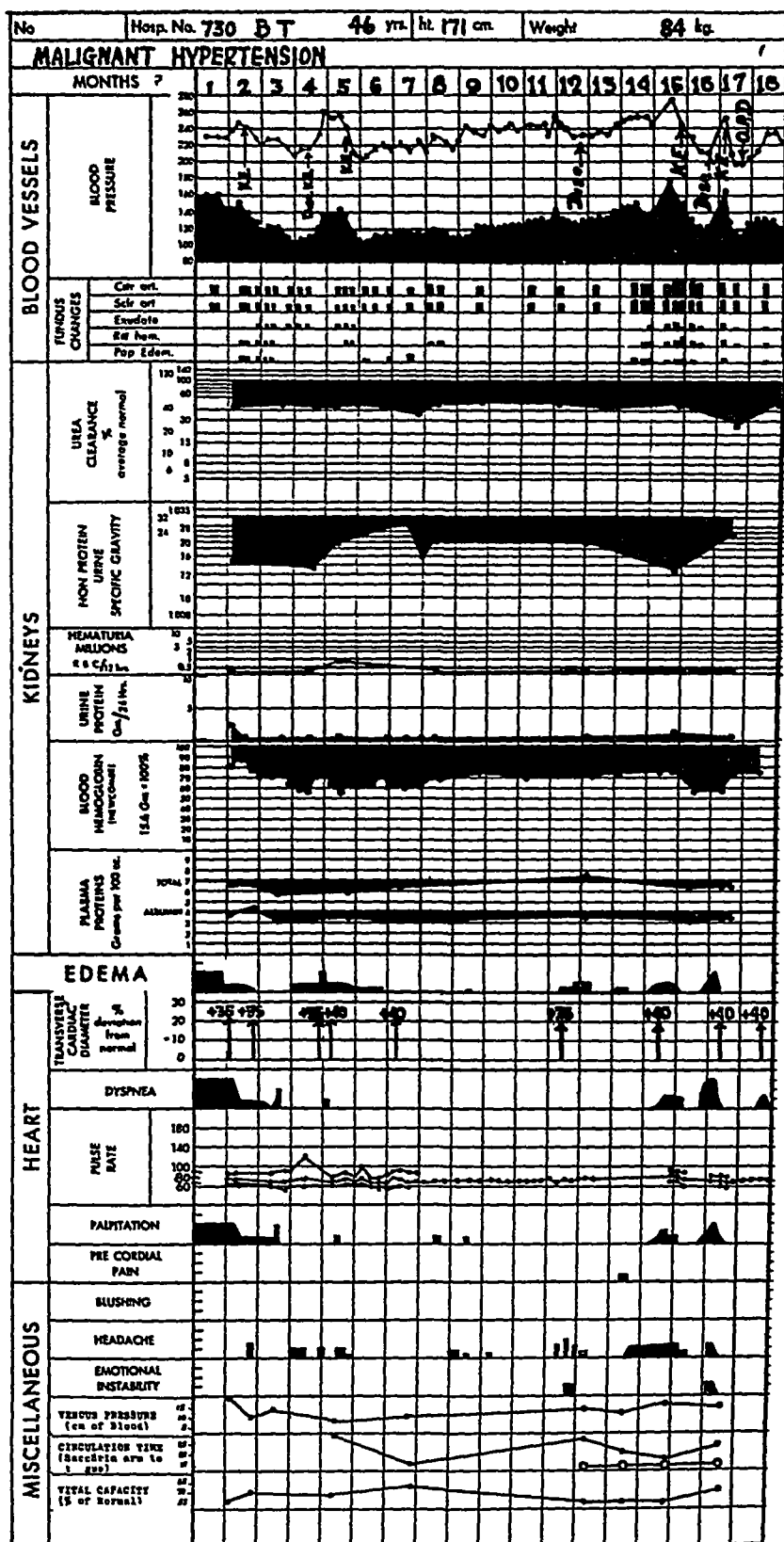


FIG 4 Example of a patient with malignant hypertension treated at various times with different extracts of kidneys. Each time extract was discontinued the average blood pressure rose.

hypertensives On the contrary, angiotonin elicits hypertension with little or no discomfort even when the appearance of the tracing is closely similar to that characteristic of patients with hypertension

We have measured the size of the hearts of our hypertensive patients under treatment by means of roentgenograms, and from these calculated the percentage deviation from normal, using the Ungerleider-Clark tables Occasionally decrease in size is observed but for the most part no change occurs even after a year or more During the normal course of events without treatment, a significant increase would have been anticipated It is our opinion that reduction in arterial pressure retards development of cardiac enlargement

The changes in the electrocardiogram are interesting, especially the reversal of the T-waves from a downward to upright position Of 17 patients with the malignant syndrome with T-waves inverted, 11 became upright after treatment and six showed no change Ten patients with essential hypertension exhibited inverted T-wave and six of these became upright after treatment

4 Effect on Kidneys Apparently as the result of renal arteriolosclerosis or necrosis or both, patients suffering from hypertension nearly always show some impairment of functioning tubular secretory mass (Tm_D) and concentrating power (Corcoran and Page^{8b}), and, in addition, the majority show evidence of ischemia of the residual tubular tissue This ischemia of functioning tissue is apparently associated with constriction of the glomerular efferent arterioles (Goldring, Ranges, Chasis and Smith⁹) The renal functional changes of hypertension are, therefore, consistent with the view that they arise on the one hand from arteriolosclerosis, the result of increased arterial pressure (Wilson and Byrom¹⁰) and, on the other from the unopposed action of angiotonin (Corcoran and Page¹¹)

The therapeutic action of renal extracts, if dependent upon the neutralization or destruction of angiotonin, would, from these premises, be exercised largely in decreasing the angiotonin-like intrarenal vasoconstriction and, because of the decrease of arterial pressure, in attenuating the progress of renal tissue destruction Unequivocal demonstration of both of these actions is complicated by the fact that pyrogenic materials, such as unpurified inulin or typhoid vaccine, cause acute increases of renal blood flow due largely to efferent vasodilation (Chasis, Ranges, Goldring, and Smith¹²), and may, in addition, temporarily decrease arterial pressure in hypertensive patients The measurements of renal functional changes during treatment with renal extracts were, therefore, made only in subjects whose temperature variations could be observed and the results obtained in recently (24 hours) febrile patients or dogs excluded from consideration In normal and hypertensive dogs and in human beings suffering from essential hypertension the effect of treatment with renal extracts was, in every case, a decrease of glomerular efferent arteriolar tone and, in most instances, an

associated increase of functionally effective renal blood flow, i.e., changes consistent with inhibition of the renal action of angiotonin (Corcoran and Page¹³) No evidence of regeneration of tubular secretory mass (Tm_D) was obtained, but significantly, in nearly every instance, further loss of tubular tissue did not occur

The interpretability of these observations has been increased by applications of formulae (Lamport¹⁴) dealing with renal hemodynamic changes in terms which permit comparison of data obtained in patients with varying levels of arterial pressure, anemia and plasma proteins Briefly, in a group of 20 patients, 17 of whom suffered from malignant hypertension, the mean of systolic and diastolic arterial pressures decreased from 184 to 143 mm Hg in observations made before and during treatment, whereas renal blood flow increased from 17 to 20.5 c.c. per minute per unit of functioning secretory tubular mass (Tm_D) The increase of renal blood flow during a *decrease* of arterial pressure denotes a decrease of calculated renal resistance of about 40 per cent Perhaps significantly, efferent arteriolar resistance returned during treatment to levels which only slightly exceeded the normal, while afferent arteriolar resistance, although decreased, remained at a higher level This residue of afferent arteriolar resistance may conceivably express structural changes in the afferent arterioles which remain unaffected by the inhibitor of angiotonin

The changes in individual patients are of greater interest than the mean change, which was calculated without reference to the apparent effectiveness of the extracts in use at the time of observation It should first be observed that in eight of 35 untreated patients there was no evidence of ischemia of the residual functioning tubular mass, an observation in accord with our demonstration of the absence of renal ischemia in the course of experimental renal hypertension (Corcoran and Page¹⁵) This maintenance of renal perfusion is apparently the result of equal increases of arterial pressure and renal resistance, whereas the presence of renal ischemia is associated with a disproportion in this balance In view of the increase of cardiac output (Taylor and Page^{8a}) which follows treatment with renal extracts and the resultant tendency to maintain arterial pressure at moderately increased levels, it is not surprising that in individual instances renal blood flow returned to or exceeded the normal rate in the presence of moderate residues of renal resistance In three observations renal perfusion was shown to be decreased slightly during treatment, apparently as the result of decreased arterial pressure in the presence of fixed renal resistance

DISCUSSION

Results from other laboratories are now beginning to appear in the literature Jensen, Corwin, Tolksdorf, Casey and Bauman¹⁶ were able to prepare extracts which lowered arterial pressure in rats Friedman, Jarman and Marrus¹⁷ showed clearly that kidney extract reduced the blood

pressure of rats with cellophane perinephritic hypertension to normal, whereas other substances such as erythrol tetranitrate, garlic and parsley extract, etc., were ineffective. Zichis, Wald, Thomas and Barker¹⁸ have proposed the hypothermic reaction observed in guinea pigs after injection of clinically active renal extracts as a rapid method of assay.

The process for the preparation of kidney extract has been altered from their original method by Grollman, Harrison and Williams¹⁹. Kidneys are dehydrated and dried preliminary to their extraction with acidulated water. They find the principle effective in lowering blood pressure in hypertensive rats is dialysable. When this material is concentrated it lowers the blood pressure of hypertensive rats when given by mouth just as they found their previous extracts active when given by mouth to patients. In their opinion results obtained by parenteral administration may be due merely to non-specific toxic impurities. Hence, their work is done by feeding the extracts by mouth. Their point is undoubtedly well taken. We, however, have had no experience with giving extracts by this route.

Almost nothing is known concerning the manner in which kidney extract lowers blood pressure. As discussed above, kidney extract is able to destroy angiotonin. Bing, Zucker and Perkins²⁰ found that the destruction did not occur by oxidative deamination since (a) oxygen is not necessary for the reaction, (b) destruction of angiotonin occurs without inactivation of hydroxytyramine, and (c) angiotonin is destroyed in the presence of octyl alcohol. Amine oxidase evidently is not the enzyme in the kidney which destroys angiotonin.

We have treated in the past two years, for longer or shorter periods, 37 patients of whom 24 suffered from the malignant syndrome and 13 with essential hypertension. Of the former, six died in uremia and three of cerebral hemorrhage, and of the latter none is dead. The most striking changes in the patients with the malignant syndrome were reversal of the eyeground changes with improvement of vision, changes of the inverted T-wave to an upright position, either moderate increase in renal blood flow or at least no decrease, increase in cardiac output and decrease in diastolic blood pressure. Although in the early stages pyrogenic reactions may at times have contributed to the fall in pressure, it appears doubtful that they are the main cause.

On the basis of contemporary knowledge there is reason to believe that the chief action of kidney extract is to oppose the action of angiotonin, but this certainly cannot be taken as established. It is at present a useful working hypothesis.

Both Murphy²¹ and Barker¹⁸ and their associates have prepared extracts which are active and have been used with some success in patients. Murphy²² has treated 11 patients with malignant or premalignant hypertension. Seven of the patients responded satisfactorily, two were resistant, and two were symptomatically improved without a corresponding drop in blood pressure.

SUMMARY

1 Improvement in preparation of kidney extracts has been made in that local and general reactions have been much reduced in number and severity. The yield of active material remains poor.

2 An in vitro assay method depending upon the ability of kidney extract to destroy angiotonin has been devised. There is suggestive evidence that a direct relationship exists between antipressor activity and ability to destroy angiotonin, but this has not been proved.

3 Two enzymes which destroy angiotonin (angiotonase) are contained in kidneys, one with optimal activity at about pH 4.0 and the other at about pH 7.5. The latter enzyme appears abundantly in the more active antipressor extracts.

4 A method for semiquantitative determination of the antigenic properties of kidney extract has been proposed depending upon the preparation of antiserum to a reaction-producing extract, sensitizing a guinea pig with it and ascertaining the amount of test extract required to kill the guinea pig.

5. Pyrogenic and local tissue reaction may contribute to the lowering of blood pressure in some patients but it appears unlikely to be the chief cause. It is suggested that part of the antipressor activity of kidney extract is due to its ability to neutralize angiotonin. This notion can be accepted only as a working hypothesis.

6 Kidney extract increases cardiac output in hypertensive patients when arterial pressure falls and tends to restore the contour of the ballistocardiographic curve from that usual in hypertension to normal.

7 In both hypertensive animals and man, kidney extract relaxed the efferent glomerular arteriole and this was associated in most instances with an increase of functionally effective renal blood flow, i.e., changes consistent with the inhibition of the renal action of angiotonin. No evidence of regeneration of secretory tubular cells was obtained but significantly in many cases further loss did not occur.

8 The clinical results on 37 patients of whom 24 had the malignant syndrome and 13 essential hypertension, and who have received a large variety of test lots of kidney extract, continue to be encouraging. Except for the lessening of reactions the clinical results are much the same as reported last year.

BIBLIOGRAPHY

- 1 PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., KEMPF, G. F., GAMBILL, W. D., and TAYLOR, R. D. The blood pressure reducing property of extracts of kidneys in hypertensive patients and animals, *ANN INT MED*, 1941, xv, 347.
- 2 CORCORAN, A. C., and PAGE, I. H. Observations on the relation of experimental hypertension to renal clearance and renal ischemia, *Am Jr Physiol*, 1938, cxliii, 43.
- 3 BING, R. J. The formation of hydroxytyramine by extracts of renal cortex and by perfused kidneys, *Am Jr Physiol*, 1941, cxxxi, 497.
- 4 PAGE, I. H. Arterial hypertension, *Jr Urol*, 1941, xli, 807.

- 5 PAGE, I H, HELMER, O M, KOHLSTAEDT, K G, FOUTS, P J, KEMPF, G F, and CORCORAN, A C Substance in kidneys and muscle eliciting prolonged reduction of blood pressure in human and experimental hypertension, *Proc Soc Exper Biol and Med*, 1940, xliii, 722
- 6 HELMER, O M, KOHLSTAEDT, K G, and PAGE, I H Destruction of angiotonin by extracts of various tissues, *Fed Proc*, 1942, i, 114
 HELMER, O M, KOHLSTAEDT, K G, KEMPF, G F, and PAGE, I H The assay of antipressor extracts of kidney by in vitro destruction of angiotonin, *Fed Proc*, 1942, i, 114
- 7 Unpublished observations
- 8 a TAYLOR, R M, and PAGE, I H The effect on cardiac output of renal extracts which lower arterial blood pressure in hypertensive patients, and of the pressor substances angiotonin, tyramine and methyl guanidine sulfate, *Proc Central Soc Clin Res*, 1941, xiv, 16
- 8 b CORCORAN, A C, and PAGE, I H Quantitative formulation of maximum urinary specific gravity, *Jr Mt Sinai Hosp*, 1938, viii, 459
- 9 GOLDRING, W, RANGES, H A, CHASIS, H, and SMITH, H W Effective renal blood flow and functional excretory tubular mass in essential hypertension, *Jr Clin Invest*, 1938, xvii, 505
- 10 WILSON, C, and BYROM, F B Renal changes in malignant hypertension, *Lancet*, 1939, i, 136
- 11 CORCORAN, A C, and PAGE, I H The effects of angiotonin on renal blood flow and glomerular filtration, *Am Jr Physiol*, 1940, cxxx, 335
- 12 CHASIS, H, RANGES, H A, GOLDRING, W, and SMITH, H W The control of renal blood flow and glomerular filtration in normal man, *Jr Clin Invest*, 1938, xvii, 683
- 13 CORCORAN, A C, and PAGE, I H The effect on renal function of renal extracts which lower arterial blood pressure in patients with essential and malignant hypertension and in dogs with experimental hypertension, *Proc Central Soc Clin Res*, 1940, xiii, 38
- 14 LAMPORT, H Formulae for afferent and efferent arteriolar resistance in the human kidney an application to the effects of spinal anesthesia, *Jr Clin Invest*, 1941, xx, 535
- 15 CORCORAN, A C, and PAGE, I H Renal blood flow in experimental renal hypertension, *Am Jr Physiol*, 1942, cxxxv, 361
- 16 JENSEN, H, CORWIN, W C, TOLKSDORF, S, CASEY, J J, and BAUMAN, F Reduction of arterial blood pressure of hypertensive rats by administration of renal extracts, *Jr Pharmacol and Exper Therap*, 1941, lxxiii, 38
- 17 FRIEDMAN, B, JARMAN, J, and MARRUS, J Therapeutic agents and renal implantations in experimental hypertension, *Jr Mt Sinai Hosp*, 1942, viii, 534
- 18 ZICHIS, J, WALD, M, THOMAS, M, and BARKER, M H The thermal effect of anti-hypertensive renal extracts on young guinea pigs, *Proc Central Soc Clin Res*, 1941, xiv, 15
- 19 GROLLMAN, A, HARRISON, T R, and WILLIAMS, J R, JR Further studies on the preparation of kidney extracts effective in reducing the blood pressure in experimental hypertensives, *Fed Proc*, 1942, i, 34
- 20 BING, R J, ZUCKER, M B, and PERKINS, W Comparison between destruction of angiotonin, hydroxytyramine and tyramine by renal extracts, *Proc Soc Exper Biol and Med*, 1941, xlviii, 372
- 21 MURPHY, F D, GRILL, J, LANGENFELD, G P, KURTEN, L J, and GUENTHER, V. The use of kidney extract in controlling experimental renal hypertension and essential hypertension, *Proc Central Soc Clin Res*, 1941, xiv, 16
- 22 MURPHY, F D Modern trends in treatment of hypertension, *Wisconsin Med Jr*, 1942, xli, 199

ILEOSTOMY FOR CHRONIC ULCERATIVE COLITIS (END RESULTS AND COMPLICATIONS IN 185 CASES) *

By J ARNOLD BARGEN, M D , F A C P , WALLACE W LINDAHL, M D ,
FRANK S ASHBURN, M D , and JOHN DEJ PEMBERTON, M D ,
Rochester, Minnesota

THE evolution of ileostomy as the foremost surgical procedure for the treatment of chronic ulcerative colitis of the thromboulcerative type has had a long and devious course. The long years during which it was being evaluated, as well as study of the cases in which it was done, brought to the fore sporadic attempts to substitute for it such maneuvers as appendicostomy, cecostomy, colostomy and ileosigmoidostomy. These operations were always eventually replaced by the seemingly inevitable ileostomy.

GENERAL CONSIDERATIONS

An attempt has been made to exercise fair and unbiased judgment on this surgical procedure by study of (1) end results for 185 patients who underwent this operation for chronic ulcerative colitis of the streptococcic type, (2) the reasons for which ileostomy was carried out and (3) the complications directly or indirectly attributable to ileostomy in such cases.

Final evaluation of any form of treatment for chronic disease must depend on prolonged observation of a fairly large group of patients. Our study included 185 patients operated on consecutively at the Mayo Clinic in the years from 1913 through 1939, or a period of 27 years. During this period 186 patients suffering from "chronic ulcerative colitis" underwent ileostomy at some time during the course of their disease. Of the entire group (186), only one patient was not traced postoperatively and this patient is not included in this study of 185 patients. The number of patients operated on each year is summarized in table 1 †. It will be noted that the number of patients who underwent ileostomy varied greatly from year to year. During the early period (1913 to 1921) ileostomy was performed more frequently than during subsequent periods. During this early period one of the reasons for performance of ileostomy was the belief that ileosigmoidostomy could be performed safely at a later date, but this was soon proved to be unsatisfactory. Later, ileostomy became the first stage of a series of operations designed to remove the entire colon. The number of patients who received this type of treatment (colectomy) was limited by the high operative risk associated with it as well as by the fact that since some

* Read before the meeting of the American College of Physicians, St. Paul, Minnesota, April 23, 1942.

† Total in table 1 is 188 patients, but only 185 are concerned in this study. See footnotes to table 1 for explanation.

of the patients had obtained sufficient relief from ileostomy alone, the subsequent performance of colectomy was not thought to be advisable. The comparatively large number of cases in which ileostomy was carried out in the years 1917 to 1926, inclusive, is expressive of the lack of adequate medical management in those years. During that period, in many cases, ileostomy was performed early in the course of the disease, or it was performed for the

TABLE I
Number of Patients Undergoing Ileostomy, 27 Years

Year	Patients Undergoing Ileostomy	Total New Patients with Chronic Ulcerative Colitis Seen
1913	1	117
1914	0	
1915	7	
1916	8	
1917	15	
1918	9	38
1919	18	40
1920	12	42
1921	6*	50
1922	9	52
1923	16	57
1924	13	63
1925	8	102
1926	12†	134
1927	3	154
1928	5‡	189
1929	8	197
1930	2	202
1931	9	140
1932	1	110
1933	0	124
1934	6	165
1935	1	175
1936	2	1150§
1937	8	
1938	4	
1939	5	
Total	188	3301

* One patient operated on in 1921 not included in text of study because she was not traced postoperatively
† One patient operated on in 1926 not included in text of study because at time of ileostomy he was found to have tuberculous enteritis with tuberculous peritonitis
‡ One patient who came to clinic in 1928 had undergone ileostomy elsewhere, and was not included in text of study
§ The figure 1150 is approximate but correct to plus or minus 10

fulminating forms of the disease, with disastrous results. It was when we encountered patients who had the fulminating forms of chronic ulcerative colitis that we used to feel that when available medical measures did not seem to achieve success, ileostomy was to be undertaken as another therapeutic measure. We believe the mortality rates accompanying such a course speak for themselves. It was never a question of performance of ileostomy as a last resort, nor was the operation itself postponed until the

patient's condition was such as to make it a most dangerous procedure. The high mortality rate associated with ileostomy for this group of patients simply bespeaks the serious nature of this particular form of colitis and the inadequacy of all forms of therapy during the early years of the struggle for control of this devastating disease.

The reader should constantly keep in mind the fact that this paper is an analytic review of a form of treatment (ileostomy) carried out during a period of 27 years. All deaths, immediate as well as late, are included in our study. In no sense is the performance of ileostomy for any given group of patients to be considered as representing immature judgment, for in every instance it was undertaken after mature and detailed consideration, by clinicians and surgeons of wide experience, of all factors in a given case. We are attempting to present frankly and critically our experiences with this form of treatment.

In recent years ileostomy has been carried out more frequently for complications of "chronic ulcerative colitis" than for other reasons. Ileostomy has been employed at the Mayo Clinic as a form of treatment for chronic ulcerative colitis for approximately 55 per cent of the total number of patients suffering from "chronic ulcerative colitis" observed in those years.

EXPLANATION OF THE GROUPING SYSTEM

Basic Plan The 185 patients were divided into three groups in regard to indications for ileostomy.

Group 1 Group 1 included 86 patients who had undergone ileostomy because of chronic progressive and intractable symptoms of ulcerative colitis without necessarily severe exacerbations.

Group 2 Group 2 included 63 patients who had the severe and fulminating forms of chronic ulcerative colitis, with acute symptoms at the time of operation.

Group 3 Group 3 included 36 patients who were operated on primarily because of complications and sequelae of ulcerative colitis.

TABLE II
Complications Considered to Be Indications for Ileostomy in
Chronic Ulcerative Colitis (36 Patients)*

Type	Number
Stricture, rectum or colon	11
Abdominal tumor, with proved or probable carcinoma	10
Incompetent anal sphincters	7
Extensive perirectal infection not responding to other treatment	7
Polyposis, colon	4
Perforation, colon	4
Massive hemorrhage, from colon	4
Intestinal obstruction	4
Total	51

* 51 complications occurred in 36 cases.

The complications considered to be indications for ileostomy in these 36 cases have been summarized in table 2, and a graphic explanation of the grouping system appears in table 3

Survival According to Definite Periods To study the records of patients from the standpoint of the length of their survival, they were divided into three periods as indicated in table 4. A more nearly accurate evaluation of the results of ileostomy was thus obtained, as well as information concerning the risk associated with the procedure. It will be noted that 35 patients lived less than 14 days after ileostomy, and that 20 patients lived more than 13 days but less than six months postoperatively. Members of the second

TABLE III
Grouping of Patients According to Indications for Ileostomy (185 Patients)

Group	Pa- tients	Condition at Time Patient Seen
1	86	Chronic, progressive, intractable symptoms without severe exacerbations
2	63	Acute symptoms of fulminating disease at the time of operation
3	36	Complications of chronic ulcerative colitis

group would seem to represent those patients who were able to withstand ileostomy but died as the result of progression of ulcerative colitis in spite of the operation.

Thus, represented in period 3 (table 4) are 130 patients concerning whom a fair study of the effect of ileostomy could be made. Among these 130 patients a study of the incidence of recurrence of symptoms of colitis and the complications arising after ileostomy could be made, since a period of six months seems sufficient for the patient to adjust himself or herself to an ileac stoma. Also among these 130 patients, a fairly accurate appraisal of the end results of ileostomy as a method of treatment could be made. A summary of this study can be obtained by inspection of tables 3 and 4. The tables show that the mortality rate among those patients who underwent ileostomy

TABLE IV
Results of Ileostomy on Basis of Length of Survival after Operation (185 Patients)

Group	Period 1		Period 2		Period 3	
	Lived Less than 14 Days		Lived Less than 6 Months but More than 13 Days		Lived More than 6 Months	
	Number	Per Cent*	Number	Per Cent*	Number	Per Cent*
1	8	22.8	4	20.0	74	56.1
2	21	60.0	13	65.0	29	22.3
3	6	17.1	3	15.0	27	20.8
Total	35	18.9†	20	10.8†	130	70.3†

* Of total number of cases in each period

† Of total number of cases in entire study.

TABLE V
Causes of Death Patients of Period 1*
(35 Patients)

Death Cause	Patients Number
Peritonitis	14
Inanition and exhaustion	6
Bronchopneumonia	5
Perforation of colon, after ileostomy	3
Inability to control diarrhea from ileac stoma	2
Postoperative shock	2
Hemorrhage from colon, after ileostomy	1
Parotitis	1
Coronary occlusion	1
Total	35

* Died within 14 days after ileostomy

while an acute exacerbation of the disease was present was roughly three times as great (except in period 3) as the mortality rate among those patients undergoing operation at a time when acute symptoms were not present or among those operated on because of complications or intractability of the disease

An analysis of the causes of death of patients in period 1 appears in table 5; of deaths of patients in period 2, in table 6

TABLE VI
Causes of Death Patients of Period 2*
(20 Patients)

Death, Cause	Patients, Number
Peritonitis	6
Progression of ulcerative colitis	5
Inanition and exhaustion	3
Pulmonary embolism	2
Further operative procedures	1
Bronchopneumonia	1
Postoperative hemorrhage from colon, after ileostomy	1
Inability to control diarrhea from ileac stoma	1
Total	20

* Lived more than 13 days and less than 6 months after ileostomy

ESSENTIAL NATURE OF THE STUDY GENERAL RESULTS

Our study then concerns itself largely with the 130 patients who survived ileostomy for more than six months. The incidence and severity of the recurrence of symptoms of colitis after ileostomy were studied among the 130 patients who survived this period. It would seem that those patients who would respond to this form of therapy would have had sufficient time in which to adjust themselves to the changes which follow ileostomy. The

condition of the patients was graded on the basis of 1 to 4, depending upon the severity of the recurrence of symptoms of colitis (table 7). The condition of these 130 patients was influenced in several instances by the performance of other types of operations after ileostomy

It is seen, then, that only 79 of the 185 patients derived real benefit from ileostomy. Of the 37 patients whose subsequent symptoms were of grade 1 (table 7), seven underwent other operations after ileostomy. Of the 42 patients whose subsequent symptoms were of grade 2 (table 7), 10 had further surgical treatment after ileostomy. The majority of patients who underwent further surgical treatment did so because of continued intractable symptoms of colitis. In most instances the beneficial result obtained could be attributed to the fact that another type of surgical procedure followed ileostomy. This additional surgical procedure included partial or total colectomy.

TABLE VII
Incidence and Grade of Recurrent Symptoms, 130 Patients of Period 3*

Grade	Explanation of Grade	Number
1	Symptom-free, or only mild recurrent symptoms, patients satisfied	37
2	Patients had frequent symptoms of colonic disease, but were satisfied (improvement)	42
3	Patients survived for considerable time, but severe and frequent recurrence (no improvement)	25
4	Severe and frequent recurrence, death within relatively short time (no benefit from ileostomy)	26

* Survived for more than 6 months after ileostomy.

It would appear, therefore, that the incidence of recurrence of infection in the colon after ileostomy is high. Fifty-one patients, or 39.2 per cent of those who survived ileostomy for six months or longer, had severe, frequent recurrences of the disease (table 7).

COMPLICATIONS WHICH FOLLOWED ILEOSTOMY

Prolapse of Ileum Prolapse of a part of the ileum through the ileac stoma was the most common complication to arise after ileostomy. There were 27 such cases. Operative procedures performed for the correction of the prolapse resulted in the death of the patient postoperatively in four instances. One other patient died as a result of such prolapse, an operation to correct the prolapse had not been performed because the poor general condition of the patient would not permit it. This complication at times constituted the only noteworthy complaint of the patient, and was difficult to control without resort to additional surgical treatment.

Formation of Abscesses and Fistulae Abscesses and fistulae occurred in 19 instances. The fistulae usually opened into the ileum from the abdominal wall at a point on the ileum proximal to the ileac stoma. Blood, pus and fecal material drained from the fistulous openings in variable

amounts. An abscess appearing in the abdominal wall was usually the first sign of a latent fistula. Systemic reactions in the form of chills, fever, anorexia, weakness and loss of weight occurred in the course of fistula formation. Not infrequently a single patient had several abscesses within the abdominal wall. Involvement of the distal portion of the ileum by the disease process may have been a predisposing factor to the formation of abscesses and fistulae.

Intestinal Obstruction In 13 patients intestinal obstruction developed subsequent to ileostomy. Five of these patients died soon after the operation that was performed for correction of the obstruction. The poor physical condition of the patient before the onset of intestinal obstruction seemed to be a potent factor in the high mortality rate which followed surgical intervention for correction of the obstruction. The relative frequency and the high associated mortality rate of this condition depict its serious nature.

Chronic Infectious Arthritis Sixteen patients had recurrent episodes of a chronic infectious type of arthritis after ileostomy. Several patients returned to the clinic subsequent to ileostomy primarily because of this condition. All the patients suffering from arthritis had recurrent infection in the colon. Other infectious complications such as perirectal infection, abscess of the abdominal wall and formation of fistulae, pyoderma and infection of the urinary tract were frequent among these patients. In the majority of these patients no exact sequence between exacerbations of the infection in the colon and exacerbations of the arthritis could be determined. One patient who had severe recurrent exacerbations of arthritis obtained complete relief after colectomy. This patient has been entirely well (at the time of this report) for nine years after colectomy. Patients who had had arthritis before the performance of ileostomy did not appear to obtain relief from the operation. It is to be noted that among 11 of the 16 patients the first symptoms of arthritis appeared after the performance of ileostomy.

Stricture of the Rectum, Colon or Stoma Stricture of the rectum, of the colon, or at the ileac stoma occurred among 10 patients to a severe degree, but developed in a milder form in many others. In such cases purulent material drained freely from the rectum for variable periods, when suddenly, without other symptoms, drainage would subside or cease entirely and fever, chills, anorexia, abdominal pain and tenderness would occur. Surgical drainage of the colon was found necessary in some of these cases. In two cases stricture of the ileac stoma developed which was of sufficient degree to necessitate surgical intervention for relief.

Polyposis of the Colon In 13 patients polyposis of the colon occurred after the making of the ileac stoma.

Perirectal Infection Perirectal infection in the form of perirectal abscess, rectovaginal fistula or fistula-in-ano developed among nine patients after ileostomy. Twenty-four other patients had had this difficulty prior to ileostomy. Fourteen of these 24 patients seemed to have derived benefit

from ileostomy In 22 of the 24 patients the perinectal infection was considered to be one of the indications for ileostomy The results would suggest that ileostomy was a helpful form of treatment for these particular patients

Urinary Complications Urinary complications occurred among 16 patients Four patients had chronic glomerular nephritis In six cases renal stones developed and in two others typical histories of renal colic had been obtained In three urethrorectal fistulae developed Of these three patients two died within 14 months after ileostomy One of these died as a result of carcinoma of the gall-bladder with metastatic lesions, and the other died of inanition associated with further exacerbations of the colitis The third patient was alive seven years after ileostomy and during these years no improvement had occurred as to the condition of the fistula One patient suffered from recurrent attacks of cystitis

Carcinoma In six patients carcinoma developed subsequent to ileostomy In three the carcinoma occurred in the rectum, in one in the gall-bladder, in one in the ovary, and one patient died of generalized abdominal carcinomatosis of undetermined origin

Cutaneous Lesions Five patients complained of recurrent cutaneous lesions Three of these had pyoderma gangraenosum, one erythema nodosum and one dermatitis about the iliac stoma One of the patients who had suffered from pyoderma with each exacerbation of colitis prior to ileostomy had the same complication after ileostomy

Hemorrhage In nine cases hemorrhage was a prominent symptom In four of the nine cases hemorrhage was so severe that it was thought advisable to perform further surgery in order to save the patient's life Three of these four patients died postoperatively In two other patients the hemorrhage was so severe that it was thought to be the major factor contributing to the early death of these patients In this group of nine cases severe rectal hemorrhage had been a prominent symptom prior to ileostomy This would suggest that ileostomy had but little beneficial effect on the patients who had severe rectal bleeding It is worth noting that only four patients of our entire group underwent ileostomy because of severe hemorrhage, whereas nine suffered severely from hemorrhage after ileostomy. Cave^{4, 5, 6} has pointed out that "massive hemorrhage" should not be accepted as an indication for ileostomy Garlock and others, however, have considered it to be a major indication for ileostomy

Anemia A hemoglobin-deficiency type of anemia was present preoperatively in all but seven of the cases studied The average preoperative value for hemoglobin of a large group of these patients was 60 per cent of normal In a similar group studies carried out several months to years after ileostomy disclosed that the average value for hemoglobin was 64 per cent of normal Continued anemia was traced in most instances to continuation of the infective process in the colon

Miscellaneous Complications Other serious sequelae occurring among patients who had ileac stomata included leukemia, multiple sclerosis in one, cirrhosis of the liver in one, severe corneal ulcer with conjunctivitis in one, pulmonary tuberculosis in one, recurrent cholecystitis in one, and bronchiectasis in one. In two patients an ileocecal granuloma developed. Some, at least, of these lesions, may have occurred because of the infective process in the colon.*

The fact that some patients may experience serious difficulty merely because ileostomy has been performed would in itself seem to discredit the suggestion of some^{4, 7, 13} that ileostomy should be carried out early in the course of the disease.

PATIENTS WHO SURVIVED ILEOSTOMY MORE THAN FIFTEEN YEARS

In an effort to determine what sort of patient would derive most benefit from ileostomy, a study was made of 18 patients who were known to be living 15 years after ileostomy. The period of observation after ileostomy in these cases ranged from 15 to 24 years. The average follow-up period was 19 years. Ten patients were females and eight were males. The average age of these patients at the time of performance of ileostomy was 32 years. The average duration of symptoms of chronic ulcerative colitis prior to ileostomy was four and a half years, but in individual cases the duration varied from one to 15 years. Thirteen patients underwent ileostomy because they had had intractable symptoms, but without severe exacerbations. Four patients were operated upon for an acute exacerbation of the disease, one for rectal stricture and persistent symptoms of perirectal infection. Seven of the 18 patients had undergone colectomy after ileostomy. Two of these seven patients had undergone total colectomy with removal of the rectum, five had undergone subtotal colectomy, that is, removal of the large intestine as far as the rectosigmoid junction.

Several factors seemed to be responsible for the satisfactory results obtained for this small group of patients: (1) the majority of these patients had had the disease for a relatively short time, (2) the patients were young adults and thus were able to adjust their lives to the handicaps imposed by the performance of ileostomy, (3) most of the patients were operated on for chronic intractable symptoms and not acute exacerbations of the disease and (4) the survival after colectomy in itself removed the opportunity for any further development or existence of colonic disease in seven of the 18 patients.

COLECTOMY AFTER ILEOSTOMY

A portion or all of the colon was removed from 30 patients of the entire group subsequent to the performance of ileostomy. In 18 instances the entire colon was removed to as far as the rectosigmoid region. In five cases

*The number of complications in this section exceeds the number of patients because some patients had more than one complication.

the cecum, ascending portion of the colon, and a portion of the transverse colon were removed, in four the entire colon, including the rectum, was removed. From two patients the terminal portion of the ileum, the cecum, ascending part of the colon and a portion of the transverse colon were removed, with the performance of ileosigmoidostomy at the time of removal of the colon. One patient underwent abdominoperineal resection of the rectum for carcinoma. Of the 30 patients operated on in this particular group, 11 died during the immediate postoperative period.

It might be assumed on the basis of the foregoing that the risk of colectomy is prohibitive, but it should be remembered that operations in this group were performed in the years from 1913 to 1940. Moreover, as more experience has accrued in the selection of patients for colectomy and in the proper choice of the time at which to do colectomy in individual cases, and as marked advances have been made in preoperative and postoperative

TABLE VIII
Colectomy after Ileostomy Type of Operation, Deaths (30 Patients)

Operation	Number	Died Post-operatively
Total colectomy with removal of the rectum*	4	0
Colectomy including the entire colon to the rectosigmoid*	18	7
Resection of cecum, ascending colon, a part of the transverse colon and the terminal ileum	5	3
Resection of cecum, ascending colon and a part of the transverse colon with ileosigmoidostomy	2	0
Abdominoperineal resection	1	1
Total	30	11

* In these cases, in most instances, removal of the bowel was accomplished by multiple operations.

care, the mortality rates accompanying this operation have been greatly reduced. This statement is in general agreement with the views of others of more recent experience^{2, 3, 4, 5, 6, 8, 9, 10}. In well-selected cases colectomy will be not only the treatment of choice but also the only satisfactory treatment. Ten of the 18 patients from whom the colon was removed to as far as the rectosigmoid and four who underwent removal of the entire large intestine were in good health for from two to 20 years after such removal. Data concerning the 30 patients in this group are presented in table 8.

ILEOCOLOSTOMY

In 20 cases ileostomy was followed by ileocolostomy and subsequent closure of the ileac stoma. In seven of these cases the patient's symptoms were completely relieved. The average follow-up period in these cases was six years. The nature of the colitis in these cases is not clear, but as a review of the records was made, necessarily years later, the impression was gained that in some of the earlier of the 20 cases, at least, the colitis may not

have been of the streptococcic type. In two of them, however, the patients seemed to be well and had remained so to the time of this report. Five of the patients were operated on in the years 1915 and 1916. During this time roentgenologic investigation of the colon was not nearly so accurate as it is today. Nine of the 20 patients had a recurrence of colitis within a short period after ileocolostomy. Four of the patients who had a recurrence of colitis died within 12 years after operation. One patient was alive 20 years after ileocolostomy, in spite of recurrent symptoms. Four of the 20 patients died of postoperative complications.

It can be seen, then, that eight of the 20 patients in this particular group were dead within 12 years after operation. Five other patients were known to be alive within this period, but with a recurrence of colitis during a subsequent period of observation averaging eight years. Seven other patients were completely relieved of their symptoms during a period of observation averaging six years.

Because of the poor results obtained from ileosigmoidostomy for ulcerative colitis, the operation has been attempted after ileostomy only six times since 1921. The reason for this is that prior to consideration of ileosigmoidostomy, patients have been carefully examined for any signs of active inflammation in the colon, and if such signs are encountered, the patient concerned is not considered to be suitable for the operation. The mortality rate and the recurrence of colitis both are high when the operation necessitates cutting through an actively diseased portion of bowel.

ILEOSTOMY FOR PATIENTS WHO HAVE UNDERGONE PREVIOUS OPERATIONS

Twelve of the patients included in this study had undergone surgical treatment other than ileostomy before they came to the Mayo Clinic. Four had undergone appendicostomy, four had undergone colostomy, two had undergone ileosigmoidostomy (one with exclusion of the colon) and two had undergone cecostomy. In only two instances had the previous surgical procedure resulted in temporary satisfactory improvement. In these two instances the continuity of the bowel was reestablished and colitis subsequently recurred. Ileostomy was performed for each of these patients later. Nine patients survived ileostomy and three died in the immediate postoperative period. In each of the nine patients who survived ileostomy immediate improvement was noted. In the majority of these 12 cases the patients volunteered the information that they were more satisfied, as the result of ileostomy, than they had been after the previous type of operation. Among those patients who had previously undergone appendicostomy the stoma functioned poorly. There was a tendency for the colitis to recur either in the distal or proximal portions of the colon. One patient who underwent ileosigmoidostomy with isolation of the right portion of the colon had a recurrence of colitis in the isolated loop of bowel.

COMMENT

For patients who have "chronic ulcerative colitis" ileostomy is the only method of diverting the fecal stream which is practicable and which is at least reasonably satisfactory. The favorable immediate response to ileostomy of patients who have ulcerative colitis may be striking. Patients who survive the operation may gain weight and improve in general strength, so that during the immediate postoperative period the result might appear to be favorable. We thought it important, however, to study the courses of patients for a longer period than the immediate postoperative period. It is obvious that the immediate response is not of great interest because "chronic ulcerative colitis" is a disease in which remission can be obtained with the aid of other forms of therapy. The real concern is, therefore, whether or not patients are permanently benefited by the performance of ileostomy. Ileostomy for "chronic ulcerative colitis" has been discussed frequently and at length in recent years. Its value cannot be determined in a few weeks or months after it has been performed.

The procedure of early surgical intervention for "chronic ulcerative colitis," such as performance of ileostomy when minimal symptoms are at hand, has been much discussed. No one who has had much experience with this disease would subscribe to such a plan of attack. It is suggested, we believe, in the hope that after the disease has been healed the ileac stoma can be closed. In the first place, however, we wish to reemphasize our belief that "ileostomy does not cure the disease." Moreover, it should be remembered that not only does ileostomy not cure, but that the disease often actually progresses rapidly after the performance of ileostomy. Consequently, few closures will ever be attempted, and this would imply that after ileostomy has been carried out, colectomy will become advisable. Surely no one can or would advise colectomy for a patient who has colitis which is in an early stage. Thus, the return to our original premise seems inevitable: ileostomy should be reserved for those patients who have complications and for the occasional patient who has intractable ulcerative colitis. It is unthinkable that surgical intervention can or ever will replace any well-planned medical regimen, in so far as "chronic ulcerative colitis" is concerned. Conversely, it is just as inadvisable to continue the medical management of patients who have complications demanding surgical treatment. This has been well pointed out by Rosser, Dixon and others.

There is a certain group of patients who have ulcerative colitis complicated by rather severe symptoms of perirectal infection and who usually are not helped by ileostomy, but who, rather, suffer as intensely from recurrent infection after ileostomy as they did previous to the operation. It may be that it is wise to operate reasonably early for this complication. The answer to this question has not been determined, for many patients with "chronic ulcerative colitis" complicated by perirectal abscess treated medically

have been restored to normal health and the fistula, if it has not healed, has been operated on successfully later

In one case a blind loop of colon resulted because colostomy and later ileostomy were performed. This loop was left open for purposes of irrigation. Eventually, the open ends of this portion of colon were closed. Later, an exacerbation of infection in the isolated loop of colon occurred, and surgical drainage of this obstructed loop was necessary.

In one case of the acute fulminating form of ulcerative colitis colostomy was performed and then ileostomy was carried out, but the patient died of a progressive type of toxemia. This illustrates again the futility of surgical intervention in this form of the disease.

So-called single-barrel ileostomy was performed for one patient, and the distal segment of ileum was turned into the cecum. Stricture of the colon subsequently developed, and it was necessary surgically to drain the purulent material that had collected in the colon.

The mental reactions of these patients toward their ileac stoma were carefully observed when they returned to the clinic for observation postoperatively. Many patients had received the impression that the operation had been meant to cure them of their disease. Consequently, patients often returned clamoring for closure of their ileac stoma. Common reasons for this request were freedom from symptoms, inability of patients to adjust themselves to the ileac stoma, a belief that they could not carry on social activities as they had before ileostomy, contemplation of marriage and, in some cases, the fact that patients had been told that closure might be hoped for after the symptoms of colitis had subsided. In the great majority of cases a badly scarred and contracted colon remained, and the possibility of a recurrence of infection was at hand at the time the patients returned for reexamination. For this reason the continuity of the bowel was only very rarely restored.

Study of the records of patients who died soon after ileostomy impresses the investigator with the fact that when severe symptoms are present, such patients are very poor surgical risks.

Results of the studies carried out for this review would suggest that if and when the condition of a patient suffering from ulcerative colitis reaches the stage in which ileostomy seems to be advisable or necessary, the performance of colectomy subsequent to ileostomy should be seriously considered.

The fact should be kept in mind that this study is an analysis of a single measure of therapy for one of the most devastating afflictions which can attack the human body, and that the failure of ileostomy in individual cases never should be ascribed to improper application of the operation, but rather to the intractable nature of the malady for which it was attempted.

REFERENCES

- 1 BARGEN, J. A., and DIXON, C. F. Essential operations for chronic ulcerative colitis, *Ohio State Med. J.*, 1936, xxxii, 650-653.
- 2 CATTELL, R. B. Colectomy for intractable ulcerative colitis, *Surg. Clin. North Am.*, 1937, xvii, 803-814.

- 3 CATTELL, R B The surgical treatment of ulcerative colitis, Bull Lahey Clin, 1939, 1, 2-10
- 4 CAVE, H W Surgical management of chronic intractable ulcerative colitis, Am Jr Surg, 1939, xlii, 79-82
- 5 CAVE, H W, and MACKIE, T T Chronic ulcerative colitis, South Med Jr, 1938, xxxi, 414-417
- 6 CAVE, H W, and NICKEL, W F, JR Ileostomy, Ann Surg, 1940, cxii, 747-757
- 7 FIROR Personal communication to the authors
- 8 GARLOCK, H H The surgical treatment of intractable ulcerative colitis, Ann Surg, 1941, cxiii, 2-14
- 9 JONES, T E The surgical treatment of ulcerative colitis, Jr Am Med Assoc, 1938, cxi, 2076-2078
- 10 MCKITTRICK, L S, and MIDLER, R H Idiopathic ulcerative colitis a review of 149 cases with particular reference to the value of, and indications for surgical treatment, Ann Surg, 1935, cli, 656-668.
- 11 RANKIN, F W Surgery for ulcerative colitis, Surg, Gynec and Obst, 1939, lxxviii, 306-313.
- 12 ROSSER, CURTICE Essential surgery in chronic ulcerative colitis, Am Jr Surg, 1932, xvii, 360-363
- 13 STRAUSS, ALFRED Personal communication to the authors

PROPHYLACTIC AND THERAPEUTIC DETOXICATION

GUANIDINE, INDOLE AND HISTAMINE *

By GUSTAV J MARTIN, E H RENNEBAUM, and MARVIN R THOMPSON,
New York, N Y

INTRODUCTION

INDOLE, histamine and guanidine are representative examples of toxic chemicals produced endogenously. These compounds were considered as a group not only because of their endogenous origin but also because each is associated with diseases known to afflict the human body. No study of therapeutic and prophylactic detoxication would be complete without a consideration of these toxic metabolites. It is to be emphasized that each is a representative of a group of toxic substances and that there is a large number of additional groups of toxic metabolites.

Histamine is formed through the action of putrefactive bacteria on histidine¹. It has been shown that a bacillus is present in the intestinal contents which is capable of decarboxylating histidine. Hanke and Koessler,² in an examination of 26 human stools, found 16 to contain such a micro-organism. Histamine has been isolated from intestinal contents as well as from loops of the large and small intestine. Hanke and Koessler found 500 to 600 grams of feces from normal individuals to contain 6 mg. to 20 mg. of histamine. When injected intravenously, histamine is toxic, even in small amounts, producing a condition simulating traumatic or surgical shock. When given by mouth, however, it is relatively inert, large amounts being tolerated. The histamine is destroyed by an enzyme, histaminase, described by Best.³ It has been suggested that histaminase of intestinal mucosa serves as a protection against the small amounts of histamine which normally might be formed. It is an open question whether or not histamine formed in intestinal putrefaction can be a factor in systemic intoxications. Other members of this group are the ptomaines: cadaverine formed from lysine and putresine formed from arginine.

The toxemic theory of shock, a controversial issue, must be considered. Cannon⁴ seemed to have placed the toxemic theory upon a logical basis, but more recently Blalock and his associates⁵ have seriously questioned it. The most recent work of Moon and Kennedy⁶ demonstrates the possibility of a toxic factor playing a causative rôle in certain instances in shock. In anaphylactic shock, in contrast to the secondary shock mentioned above, histamine is on a more firm basis as an etiological factor. Asthmatic at-

* Received for publication October 31, 1941

Presented in part before American Chemical Society, St. Louis, April, 1941
From the Warner Institute for Therapeutic Research, New York, N Y

tacks may be caused by histamine liberation into the blood stream. The severe though brief headache which follows the intravenous administration of histamine can be cited in support of possible involvement of this compound in headaches of the vascular type. Spriggs⁷ suggests that migraine headaches are due to liberation of histamine with consequent vasodilatation and localized edema.

Immunity of the body to autointoxication applies only to the large intestine, an autointoxication from the small intestine is probable.

The abrupt fall of systemic blood pressure which results when non-coagulant venoms are injected intravenously results in a large part from the action of phosphatidase by the formation of lysolecithin and the liberation of histamine. Arthus⁸ studied this hypotensive effect and noted its resemblance to that occurring in acute anaphylaxis in the rabbit and dog.

Feldberg and Kellaway⁹ found that the injection of the venom of *Crotalus atrox*, of *Demsoma superba* or of the Indian cobra into the pulmonary artery of the perfused guinea pig's lung caused the appearance of histamine and coagulable protein in the venous perfusate. The effect of the intravenous administration of venoms can be largely explained on a basis of histamine liberation.

Thus, the probable involvement of histamine or related substances in surgical shock, anaphylactic shock, headaches, asthma, snakebite and other conditions has been established or indicated. It is, therefore, obvious that any means of altering the toxicity of histamine endogenously is important.

Indole is a product of intestinal putrefaction which affects the aromatic amino acids. The disagreeable and characteristic odor of feces is said to be due partly to two compounds, namely indole and skatole. Indole is oxidized and conjugated with the sulfonic acid radical to form indican.

Indole when given to the human subject by mouth causes dizziness and headache. Toxic doses of this substance are prevented from entering the systemic circulation by the barrier of the gut wall or through the detoxicating action of the liver. It is a known fact that certain individuals excrete large quantities of indican in the urine, which is indicative of excessive intestinal putrefaction.

Guanidine is another product of intestinal putrefaction believed to be involved in many physiological disturbances. It is a normal product of creatine metabolism, and when injected into animals in large amounts causes a rise in blood pressure. It was claimed by Major and his associates¹⁰ that retention of this metabolite as evidenced by a rise in its concentration in the blood and reduced excretion in the urine could be demonstrated in hypertension. This theory has not been generally substantiated. Guanidine may play a minor rôle in parathyroid tetany, although it certainly is not the major factor. As recently as 1939, Major et al.¹¹ reported an increase in guanidine in the blood in experimental renal insufficiency which occurs both with and without accompanying hypertension. The compound may be an anhydride

of guanidine, glycoyamidine It has been suggested¹² that guanidine intoxication is a significant factor in trichinosis Dodd et al¹³ report that the concentration of guanidine in the blood increases in intestinal intoxication of infancy The outstanding symptoms of alimentary toxicosis in infancy and early childhood are intensive vomiting and diarrhea, resulting in dehydration, acidosis and circulatory collapse Mason et al¹⁴ note that guanidine occurs in blood in traces, but it is present in increased amounts in renal insufficiency and particularly in uremia Some of the symptoms of uremia are duplicated in experimental guanidine poisoning In both conditions vomiting, diarrhea, gastroenteritis, muscular twitchings, increase in blood pressure and respiratory disturbances are prominent, and, in advanced stages, apathy, stupor and circulatory collapse Guanidine appears to be a physiological antagonist of calcium, the latter inhibiting the action of guanidine on the neuromuscular apparatus In uremia, muscular twitchings may occur even when there is no central calcium deficit In such instances the effect is attributed by these workers to the action of guanidine In those cases in which a calcium deficit does exist, the muscular twitchings are more severe, presumably because there is insufficient calcium ion acting on the central nervous system to oppose adequately the effects of guanidine

In addition to the above, other compounds of intensely toxic character are formed in the large intestine as a result of the decomposition of protein by the normal bacterial flora Among such putrefactive products are phenol, cresol, skatole, ethylamine, isoethylamine, tyramine, etc The body, through the detoxication mechanisms of the liver, can usually handle these toxic materials, but innumerable clinical conditions exist in which these detoxication mechanisms are not normal, and in which these toxic materials accumulate in the blood stream and tissues In these conditions, it would obviously be desirable to speed up or facilitate the detoxication of these compounds, and it has been the objective of this work to attempt to influence the processes of detoxication by the administration of detoxifying compounds

EXPERIMENTAL TECHNIC AND RESULTS

White mice, 18 to 24 grams in weight, were used throughout these experiments Acute toxicities were studied in approximately 5,000 mice Indican excretions were studied in a series of 10 dogs With each of the three compounds considered the oral or subcutaneous L D 50 was checked It was evident from the outset that a multiplicity of factors affected the value, e g, the suspending agent used, the osmotic pressure of solutions administered orally, the diet of the mice before use, the hydrogen ion concentration of the solutions, weight of mice and the usual biological variation Each of the controllable factors received appropriate attention in all protocols throughout the study

All compounds used by the body in detoxication were regarded as potential detoxifying agents for these physiologically important compounds

Included among these compounds were cysteine, glycine, glutamine, sulfates, acetates and calcium glucuronate. A large number of other compounds of similar or unrelated structure were tried as potential detoxifying agents. In each instance in which a set of experiments included cysteine, the other sulfur-containing amino acids were also tried, namely, cystine and methionine. Frequently, the sulfur of these compounds is finally utilized in the form of sulfate, and, therefore, sodium sulfate was used to check its possible detoxifying effect. Glycine was replaced by alanine, serine, leucine, isoleucine and valine. Glucuronic acid was replaced by gluconic, 2-ketogluconic, galacturonic, mucic, saccharic, arabinic, pectic, lactic, pyruvic, glyoxallic acids. Dihydroxyacetone and all of the aldohexoses were also tried.

Acetic acid as its sodium salt, acetaldehyde, sodium lactate and sodium propionate were all tested for efficacy in supplying the acetyl radical. Xanthine, adenine and guanine were tested as representatives of the purine detoxifying action suggested by Neale and Winter¹⁵. No substitutes for glutamine were tried as none was known that might function as detoxifying agent. Its precursor, glutamic acid, however, was tested. Nicotinic acid, thiamine and a liquid yeast concentrate were tried, as reports¹⁶ have appeared in the literature suggesting possible detoxifying effect. Lecithin, cephalin and cholesterol were tried as positive detoxifying substances. Choline was included as a contributor of labile methyl radicals.

In the early experiments, gum arabic in 10 per cent concentration was used as a suspending agent, but frequent unexplainable variations in control toxicity determinations led us to abandon gum arabic in favor of gum tragacanth at 0.5 per cent. Gum arabic, the crude material, occurs in every state of partial hydrolysis, and as one of the products of the hydrolysis of gum arabic is glucuronic acid, a detoxifying substance, we abandoned the use of this material entirely. The use of several control sets in each experimental group even in our earlier experiments prevented any misinterpretation of results. Volumes of material for oral administration were held below 0.8 c.c. In some studies the toxic material and the detoxifying chemical or chemicals were given in the same solution. In others the toxic material was given subcutaneously and the detoxifying substances were given orally. Oral administrations were made with a long blunt syringe needle and a tuberculin syringe graduated in 0.01 c.c. No group of animals less than 25 in number was considered, and no greater variations in weight than 4 to 6 grams in any set of 250 were permitted. The dietary régime of the mice before use was controlled by maintaining them on a stock ration for several days before use and then placing the mice on an unpolished rice ration for three days before use. This latter diet is a maintenance ration, calorically adequate but inadequate nutritionally for other than maintenance. Diet before use is a most important factor. Diet variation can cause experimental results to vary by as much as 50 per cent. This is a factor which has been all too frequently neglected in a consideration of control factors in acute toxicity experiments.

TABLE I

Action of Various Physiological Detoxifying Agents and Combinations of These Agents against Acutely Toxic Dosage of Guanidine, Indole or Histamine

Compound	Detoxifying Action with Guanidine	Detoxifying Action with Indole	Detoxifying Action with Histamine
Cysteine	+	+	±
Cystine	+	+	±
Methionine	++	+	±
Glycine	+	±	-
Alanine	-	-	-
Serine	-	-	-
Leucine	-	-	-
Isoleucine	-	-	-
Valine	-	-	-
Glutamic	-	-	-
Glucuronic	+	++	+
Gluconic	±	-	-
2-ketogluconic	-	-	-
Galacturonic	±	-	-
Mucic	-	-	-
Saccharic	-	-	-
Arabinic	-	-	-
Pectic	-	-	-
Lactic	-	-	-
Pyruvic	-	-	-
Glyoxallic	-	-	-
Dihydroxyacetone	-	-	-
Acetic	-	-	-
Acetaldehyde	-	-	-
Lactic	-	-	-
Propionic	-	-	-
Aldohexoses	-	-	-
Lecithin	±	-	-
Cholesterol	-	-	-
Cephalin	-	-	-
Guanine	-	-	-
Adenine	-	-	-
Xanthine	-	-	-
Nicotinic	++	-	-
Thiamine	-	-	-
Liquid Yeast	-	-	-
Ascorbic Acid	+	±	+
Glutamine	-	-	-
Choline	++	+	-
Sulfates	-	-	-
Ornithine	-	-	-
Aldobionic	±	±	±
Saccharolactone	-	-	-
Isoascorbic	±	±	-
Glucuronic	+	+	-
Ferrous Chloride	-	-	-
Cystine	++	++	++
Glycine	++	++	++
Glucuronic	++	++	++
Ascorbic	++	++	++
Cysteine	++	++	++
Glutamic	++	++	++
Glycine	++	++	++
Ascorbic	++	++	++
Glucuronic	++	++	++
Glycine	++	++	++
Cystine	++	++	++
Glucuronic	+++	++	+
Ascorbic	+++	++	+
Nicotinic	+++	++	+
Cystine	+++	++	+
Glycine	+++	++	++
Glucuronic	+++	++	++
Ascorbic	+++	++	++
Choline	+++	++	++

Table 1 presents a summary of the results obtained with various compounds and combinations of compounds in detoxifying histamine, guanidine and indole

A consideration of table 1 clearly indicates that those compounds influencing the acute toxicity of histamine, indole or guanidine are the same compounds which the body normally uses in the processes of detoxication, cystine or one of the other sulfur-containing amino acids (cysteine or methionine), glucuronic acid, glycine, and ascorbic acid being the more commonly known detoxifying agents To this list choline must be added

TABLE II
Protocol of a Histamine Detoxication Series
(Values expressed in grams)

Compound	Preparation				
	No 1	No 2	No 3	No 4	No 5
Histamine	2 8	—	—	—	—
Tragacanth Gum	—	0 25	0 25	0 25	0 25
Cystine	—	1 0	—	—	—
Glycine	—	1 0	1 0	—	—
Ascorbic Acid	—	1 0	—	1 0	—
Calcium Glucuronate	—	1 0	—	—	1 0
Volume	140 0 c c	50 0 c c	50 0 c c	50 0 c c	50 0 c c

0 6 gram/Kilo = L D 50 Subcutaneous

Solution No 1 contains 20 0 mg of histamine per c c

Detoxifying chemical or chemicals given orally 2 to 3 hours before histamine is given

Set	Number of Mice	Weight of Mice	Oral Dose Detoxifying Preparation	Preparation Number	Subcutaneous Histamine Dose	Number Dead	Per Cent Dead
1	50	18 gm	—	—	0 54 c c	30	60
2	50	18 gm	0 7 c c	2	0 54 c c	9	18
3	50	18 gm	0 7 c c	3	0 54 c c	26	52
4	50	18 gm	0 7 c c	4	0 54 c c	20	40
5	50	18 gm	0 7 c c	5	0 54 c c	23	46

Choline has not been generally regarded as a detoxifying agent, but its action as a source of labile methyl would make it so

Tables 2, 3, and 4 present protocols of single unit experiments with each of the toxic substances histamine, indole and guanidine

These tables are presented to clarify the methods of experimentation which are difficult to describe without the aid of such protocols In each of these sets the maintenance ration was given for three days before the mice were used It was felt that, inasmuch as indole and guanidine were produced in the intestine, oral tests were indicated Histamine on the other hand is produced both in the intestine and in the tissues, hence subcutaneous tests were used

Table 2 demonstrates a reduction in the percentage of deaths following

acutely toxic doses of histamine ranging from 8 per cent to 50 per cent. In this instance the toxic material was given subcutaneously, and the detoxifying chemicals were given orally. Table 3 demonstrates a reduction in the percentage of deaths following acutely toxic doses of guanidine acetate ranging from 8 per cent to 52 per cent. Finally, table 4 demonstrates a reduction in deaths due to acutely toxic doses of indole ranging from 0 to 24 per cent.

In an attempt to explain this marked effect in acute toxicity studies, the detoxified form of indole, indican, was determined in the urine of dogs following one gram doses of indole with and without the simultaneous ad-

TABLE III
Protocol of a Guanidine Detoxication
(Values expressed in grams)

Compound	Preparation						
	No 1	No 2	No 3	No 4	No 5	No 6	No 7
Guanidine Acetate	1 25	1 25	1 25	1 25	1 25	1 25	1 25
Gum Tragacanth	0 25	0 25	0 25	0 25	0 25	0 25	0 25
Glycine	—	0 5	—	—	—	—	0 5
Cystine	—	—	0 5	—	—	—	0 5
Calcium Glucuronate	—	—	—	0 5	—	—	0 5
Ascorbic Acid	—	—	—	—	0 5	—	0 5
Nicotinic Acid	—	—	—	—	—	0 5	0 5
Volume	25 0 c c	25 0 c c	25 0 c c	25 0 c c	25 0 c c	25 0 c c	25 0 c c

0 6 gram of Guanidine Acetate per Kilo = L D 50 oral
50 0 mg of Guanidine Acetate per each 1 c c

Set	Number of Mice	Weight of Mice	Weight Dose Guanidine	Volume Dose of Preparation	Solution	Number Dead	Per Cent Dead
1	50	18 gm	10 8 mg	0 21 c c	No 1	30	60
2	50	18 gm	10 8 mg	0 21 c c	No 2	26	52
3	50	18 gm	10 8 mg	0 21 c c	No 3	20	40
4	50	18 gm	10 8 mg	0 21 c c	No 4	26	52
5	50	18 gm	10 8 mg	0 21 c c	No 5	26	52
6	50	18 gm	10 8 mg	0 21 c c	No 6	8	16
7	50	18 gm	10 8 mg	0 21 c c	No 7	4	8

ministration of a mixture of detoxifying chemicals consisting of glycine, cystine, calcium glucuronate and ascorbic acid. The method used was that of Askenstedt¹⁷. This method is more an estimation than a determination but results check on several samples and from dog to dog. In one set of three dogs receiving indole alone, the indican value in terms of indigo was 79 75 mg. The first experimental set receiving the detoxicant showed a value equal to 28 70 mg. of indigo and the second set of three determinations on experimental dogs receiving indole and the detoxifying chemicals showed a value of 35 00 mg. of indigo. These values indicate mg. of indigo from 10 c c of urine. An observation in these dogs, the significance of which is not yet clear, was the black color of the urine following administration of

TABLE IV
Protocol of an Indole Detoxication Series
(Values expressed in grams)

Compound	Preparation						
	No 1	No 2	No 3	No 4	No 5	No 6	No 7
Indole	3 75	—	—	—	—	—	—
Gum Tragacanth	0 37	0 25	0 25	0 25	0 25	0 25	0 25
Cystine	—	1 0	1 0	—	—	—	—
Glycine	—	1 0	—	1 0	—	—	—
Calcium Glucuronate	—	1 0	—	—	1 0	—	—
Ascorbic Acid	—	1 0	—	—	—	1 0	—
Choline	—	—	—	—	—	—	1 0
Volume	75 0 c c	50 0 c c	50 0 c c	50 0 c c	50 0 c c	50 0 c c	50 0 c c

0 5 gram of Indole per Kilo = L D 50 Oral

50 0 mg of Indole = 1 c c of Preparation No 1

Dose of detoxifying substance given orally 3 to 4 hours before indole was administered

Set	Number of Mice	Weight of Mice	Volume Dose Detoxifying Chemical	Preparation Number	Weight Dose Indole	Volume Dose Indole	Number Dead	Per Cent Dead
1	25	18 gm	—	—	9 mg	0 18 c c	17	68
2	25	18 gm	0 5 c c	2	9 mg	0 18 c c	9	36
3	25	18 gm	0 5 c c	3	9 mg	0 18 c c	10	40
4	25	18 gm	0 5 c c	4	9 mg	0 18 c c	17	68
5	25	18 gm	0 5 c c	5	9 mg	0 18 c c	8	32
6	25	18 gm	0 5 c c	6	9 mg.	0 18 c c	18	72
7	25	18 gm	0 5 c c	7	9 mg	0 18 c c	9	36

indole unless the detoxifying chemicals were given simultaneously, in which event the color of the urine was normal. This black urine is seen following the ingestion of certain hydrocarbons, naphthalene, and most phenolic type compounds. In the case of phenol the coloration is due to the formation of hydroquinone or pyrocatechin or, generally speaking, the dihydroxybenzenes.

DISCUSSION

The action of detoxifying chemicals is not specific for the endogenously produced poisons under consideration in this paper but rather is a manifestation of a reinforcement of the processes used by the body in its defense against toxic chemicals, regardless of their nature. This type of therapeutic or prophylactic detoxication is equally effective against the products of the metabolism of the organisms which infect the body and the specific chemotherapeutic agents used in the treatment of disease,¹⁸ as well as against a variety of poisons, to be reported separately. The problem of detoxication of absorbed toxic chemicals is the same as the problem of the detoxication of toxic chemicals produced within the body by an invading parasite. The general process of detoxication follows three lines: oxidation, reduction and

conjugation. Frequently, oxidation and reduction precede conjugation. The processes of oxidation and reduction of toxic chemicals are being subjected to intensive study, but it remains difficult to apply any practical methods of influencing these processes. Vitamin therapy doubtless owes a great deal of its effectiveness to the reestablishment of an enzyme moiety and normal processes of oxidation and reduction which are concerned in detoxication. Thus, there is available at present but one process which can be used to facilitate detoxication: namely, the process of conjugation. In passive immunity the body's defense is reinforced by supplying it with additional preformed antibodies. In conjugative detoxication it is possible to supply the body with increased raw materials used in the processes of detoxication. The mechanism of conjugative detoxication is one of enzymatic action, and in the study of enzyme action it has been found that the concentration of the substrate is a vital factor in the speed of the reaction. Starting with zero concentration of the substrate, the velocity of the reaction increases with increasing concentration of the substrate, then remains constant for a considerable variation in concentration and finally decreases in very concentrated solution of the substrate. Obviously, the concentration of the substrate in the enzymatic processes of conjugative detoxication can be altered, and this is the single factor influencing the speed of the reaction that can be altered. This immediately suggests a type of prophylaxis and therapy which is used in this paper against the acute toxication of certain chemicals.

There are several questions to be answered before the logic of this therapy can be judged. First, are the compounds involved in detoxication sufficiently well known so that an attempt could be made to reinforce them? Second, is there actually a quantitative deficiency of these compounds, or can the body supply them in unlimited amounts? Third, will an increase in the circulating amounts of these compounds actually facilitate and speed up the rate at which conjugation and detoxication occur?

Certain of the compounds involved in conjugative detoxication are well known, and no attempt will be made to review this material as various excellent reviews on the subject are available^{19, 20, 21, 22, 23, 24}. There is a certain specificity exhibited in the processes of detoxication. The compounds involved are glycine, cystine, glucuronic acid, glutamine, sulfates, acetates and ornithine. Ornithine is used only by the fowl in detoxication. Glutamine is a curiosity among detoxicating compounds, but the other above mentioned compounds are of importance in detoxication and, therefore, in vital economy.

Glycine is utilized in the detoxication of hundreds of toxic compounds. Generally, it can be stated that glycine combines with the carboxy group of organic acids. The rôle assumed by glycine can be taken over by glucuronic acid in many cases. This overlapping of specific detoxication channels is of vital significance in a rational application of detoxication in therapy and in prophylaxis. Glycine is not an essential amino acid and is not stored in

the body It is furnished as required for detoxication reactions in much greater quantities than is supplied by the food Griffith and Lewis²⁵ conclude that the rate of hippuric acid formation is directly proportional to the amount of glycine available Hippuric acid is the conjugated product of benzoic acid and glycine Experiments with both growing^{26, 27, 28} and adult animals²⁹ have shown that the rate at which the organism can produce glycine for detoxicating purposes is distinctly limited, and in a fasting man it is this factor which eventually limits the output of hippuric acid when increasing doses of sodium benzoate are ingested³⁰ Griffith and Lewis²⁵ found that the administration of glycine or protein digests rich in glycine³¹ to rabbits receiving sodium benzoate increased the rate of excretion of hippuric acid A number of other amino acids and other substances failed to produce this effect These investigators suggest that the greater rate of synthesis of this compound results from the presence of increased amounts of preformed glycine in the organism Briefly, therefore, one can state that although glycine may be synthesized in response to need for it in the detoxication reaction, an increased ratio of synthesis and excretion of a toxic substance is observed when an abundant supply of exogenous glycine is furnished Glycine has a relatively slight effect in the detoxication of the endogenous type of toxic chemicals considered here Its effect is marked in the detoxication of the sulfonamido type of chemotherapeutic agent¹⁸ A consideration of the type of compound rendered non-toxic by conjugation with glycine would lead to the conclusion that where conjugation is concerned, glycine would not detoxify histamine, guanidine or indole The slight action exerted by glycine in this study is probably due to action by way of an enzymatic system

Cysteine is a second amino acid used by the body in detoxication Generally, cystine or methionine is the qualitative but not the quantitative equivalent of cysteine Bromobenzene and other halogenated derivatives of benzene are the best known examples of compounds detoxified by combination with cysteine Cysteine hooks into the benzene ring at the para position Subsequently, the amino group of the cysteine is acetylated and the compound is then excreted The body cannot synthesize the sulfur-containing amino acids, and, therefore, they are necessary components of the diet Abderhalden's experiments on fasting dogs showed that the small amount of endogenous cystine is immediately used for such body needs as the formation of glutathione, taurine, and insulin³² More recently, White and Lewis³³ have studied the metabolism of bromobenzene in dogs on a cystine deficient protein diet and cystine rich protein diet, and they found that mercapturic acid formation parallels the cystine content of the protein Stekol³⁴ has presented evidence indicating that the organism can supply cystine to detoxicate bromobenzene at the expense of its own tissues if no exogenous cystine or methionine is available It is obvious that a distinct limit exists beyond which contributions of cystine for purposes of detoxication from the tissue of the body will result in a complete upset of body economy White

and Jackson³⁵ have utilized bromobenzene in growth experiments in which they found that when this substance was incorporated in an otherwise adequate diet, the growth of white rats was retarded. The addition of either cystine or methionine readily overcame this retarding influence. This leads to the obvious conclusion that if the body is forced to deprive itself of its tissue cystine for purposes of detoxication, other vital functions involving cystine, such as growth, must suffer. Taurine and sodium sulfate failed to stimulate growth in animals fed bromobenzene. It seems that the sulfur-containing amino acids were specific in this respect. It is clear from the above that the detoxication of bromobenzene and other toxic chemicals takes precedence over growth requirements. The mode of action of sulfur-containing amino acids is doubtless through a sulfhydryl group. Cysteine, cystine or methionine are effective in the detoxication of any one of the three compounds herein considered (guanidine, indole and histamine). Here again, the potentialities of conjugative detoxication are remote. The sulfur-containing amino acids are regarded as the source of the sulfuric radical involved in the detoxication of indole by the formation of indican. In this instance we have demonstrated that the detoxifying chemicals actually inhibit the formation of indican rather than promote it. It is, however, highly probable that the detoxication may proceed by conjugation resulting in an as yet undetermined product. Our results show that methionine possesses a somewhat greater power as a detoxifying agent than does cystine or cysteine. The labile methyl supplied by the methionine may be responsible for this increment in detoxifying power. Both choline and methionine seem to function as sources of labile methyl, and choline and methionine both act in the detoxication of indole, hence, the conclusion that labile methyl explains the greater efficiency of methionine as compared to the other sulfur-containing amino acids. It can be stated that the sulfur-containing amino acids are effective in decreasing the acute toxicity of guanidine, histamine and indole. Again, whether this effect is due to conjugation, restoration of enzymatic activity, etc., it is not possible to state at the present time.

Glucuronic acid is the conjugating agent in an almost unlimited number of instances. The compounds usually have hydroxy groups or are aldehydes or ketones which through reduction are converted into primary or secondary alcohols. Glucuronic acid is quite capable of combining with organic acids, such as benzoic, etc. The glucuronic acid conjugates are particularly interesting since one is an ester type and the other is a glucoside linkage. All recent studies tend to show that glucuronic acid plays a much greater rôle in detoxication than was formerly thought. Quick³⁶ first isolated pure glucuronic acid compounds from the urine. Hemingway, Pryde and Williams³⁷ proved that conjugation with glucuronic acid occurred in the liver. In the present study, dihydroxyacetone, pyruvic acid and lactic acid were checked for detoxifying power because of the studies of Lipschitz and Bueding³⁸. These workers demonstrated that surviving liver slices of

rabbits, rats or guinea pigs produced conjugated glucuronic acids from d-borneol, 1-menthol, avertin or phenol. The production in the liver slices was increased by insulin and depressed by adrenalin. Glucuronic acid is, therefore, not a product generated by oxidation of carbohydrates, glucosides or maltosides, nor is free glucuronic acid conjugated freely with alcohols. The formation of conjugated glucuronic acids is, according to these investigators, a synthetic process from shorter carbon chains. Two further points are emphasized by these workers, namely that heavy metal catalyzes the formation of the glucuronates, and that phosphorylation is essential to the entire process. Dihydroxyacetone, lactic acid and pyruvic acid have no effect in the detoxication of the three compounds herein considered. Glucuronic acid on the other hand is effective against histamine, indole and guanidine. With the exception of indole, the toxicity of the other two compounds is probably counteracted by glucuronic acid through enzymatic systems rather than through conjugation. In the case of indole, it is suggested that the demonstrated decreased formation of indican would indicate conjugation along other lines, namely, to a glucuronic acid product.

Evidence of the importance of vitamin C in detoxication processes is extensive. It is well known that tissue concentration of vitamin C is markedly lowered by some of the bacterial toxins and other toxic materials, and that there is a reduced tolerance for such substances by animals whose vitamin C reserves are depleted. Ascorbic acid has frequently been indirectly connected with resistance to, or the detoxication of, histamine. Epstein³⁹ noted that large doses of vitamin C aided in the desensitization of patients suffering with bronchial asthma. Lemke⁴⁰ reported that vitamin C, when injected intravenously, into hypersensitive guinea pigs, desensitizes them. Hochwald⁴¹ confirmed the observations of Lemke. Further extension of this effect of vitamin C in decreasing or abolishing the anaphylactic reaction was carried out by Hasimoto et al⁴². More recently, Yokoyama⁴³ reported that anaphylactic shock was prevented in sensitized guinea pigs by the injection of ascorbic acid immediately before the second injection of horse serum. If the horse serum was mixed with the ascorbic acid before injection, shock was also prevented, probably owing to the denaturation of the antigen. The Schultz Dale reaction of isolated intestine from sensitized guinea pigs was inhibited by vitamin C if it was added to the Locke solution five minutes before the horse serum. In similar conditions a slight reaction was obtained with isolated uterus, but it is considered that uterine muscle is more sensitive than intestinal. Raffel and Madison,⁴⁴ on the other hand, report complete inhibition of hypersensitive manifestations in only two of 16 guinea pigs treated daily with ascorbic acid. In this same vein, Ungar et al⁴⁵ report that the treatment of tissues with ascorbic acid renders them less labile as regards the liberation of histamine. It seems safe to conclude that an inhibition of anaphylactic reactions does follow the administration of vitamin C and our observations, in which we have demonstrated a decrease in the acute toxicity of histamine through the

concomitant administration of ascorbic acid, would support this conclusion

The preceding discussion clearly outlines the basis for the use of the detoxifying chemicals in prophylaxis and in therapy. Approximately 50 different compounds have been used in an attempt to determine those most effective. It is clear that the most effective compounds are those used by the body in the ordinary processes of detoxication. Cystine, glycine, ascorbic acid and calcium glucuronate are the most effective, and the mixture of these chemicals is generally more effective than any single one. Each of the effective chemicals is a physiological body constituent. They are obviously in themselves non-toxic. The exact mechanism of their action is not clear. Partially, it is undoubtedly one of conjugative detoxication, and it is perhaps a mass action effect. The enzymatic processes of detoxication are facilitated by increased concentrations of the substrate, in this instance the detoxifying chemicals. It is to be noted that the major portions of these detoxifying agents are physiological reducing agents. This fact leads us to assume that a restoration of the cellular moiety necessary for enzymatic action other than that of conjugative detoxication is in part responsible for the effects observed in this study. Fundamentally, this type of therapy or of prophylaxis consists in reinforcing the body's own natural processes of defense against toxic chemicals. It is aimed primarily at detoxifying the toxic substances introduced into the body or produced endogenously.

It is strange that despite the enormous literature on the processes of detoxication, only recently has any attempt been made to develop this field of therapy and prophylaxis. It is certain that one phase of any deleterious process is the detoxication of the chemicals injuring the body, and it is also true that any procedure whereby this detoxication is speeded up will decrease the concentration of the toxic chemical present at a given time in the body and aid materially in the alleviation of the deleterious process. The entire thought behind therapeutic and prophylactic detoxication is its use as an adjuvant to specific therapy. In certain types of disease, e g, toxemia of pregnancy, in which the etiology is not known and no specific therapy has been accepted, it is suggested that results might be obtained using detoxifying chemicals.

This study is based upon the theory that the detoxication and elimination from the body of poisonous materials, of whatever nature, is accomplished by the use of chemical substances normally present in the body, the reserve supply of which is relatively limited. An attempt has been made to study the rôle played by certain of these individual substances in the process of detoxication, and also to apply this knowledge therapeutically in man and animals, in such a manner as to secure the greatest possible protection by means of their detoxifying activities.

Histamine, indole and guanidine represent groups of toxic chemicals produced endogenously. In acute toxicity experiments it has been found possible to decrease markedly the toxicity of these substances by the concomitant administration of certain physiological detoxifying agents: ascorbic

acid, glycine, glucuronic acid and cystine (sulfur-containing amino acid). Indican formation is inhibited by the use of these detoxifying agents

BIBLIOGRAPHY

- 1 ACKERMANN, D Origin of bases in putrefaction, *Ztschr f physiol Chem*, 1910, lx, 504
- 2 HANKE, M T, and KOESSLER, K K Studies of proteinogenous amines, *Jr Biol Chem*, 1924, lxx, 879-889
- 3 BEST, C H Disappearance of histamine from autolyzing lung tissue, *Jr Physiol*, 1929, lxxix, 256
- 4 CANNON, W B Consideration of possible toxic and nervous factors in production of traumatic shock, *Ann Surg*, 1934, c, 704
- 5 BLALOCK, A Experimental shock, *Arch Surg*, 1930, xx, 959
- 6 MOON, V H, and KENNEDY, P J The pathology of shock, *Arch Path*, 1932, xiv, 360
- 7 SPRIGGS, E Clinical study of headaches, *Lancet*, 1935, ii, 63
- 8 ARTHUS, M Vasomotor phenomena produced by certain venoms, *Arch internat. de physiol*, 1913, xiii, 329
- 9 FELDBERG, W, and KELLAWAY, C H Liberation of histamine from perfused lung by snake venoms, *Jr Physiol*, 1937, xc, 257
- 10 MAJOR, R H, and WEBER, C J Possible increase of guanidine in blood of certain persons with hypertension, *Arch Int Med*, 1927, xl, 891
- 11 MAJOR, R H, WEBER, C J, and RUMOLD, M J Blood "guanidine," *Arch Int Med*, 1939, lxix, 988
- 12 HARWOOD, P D, SPINDLER, L A, CROSS, S X, and CUTLER, J T Guanidine retention in experimental trichinosis in rabbits, *Am Jr Hyg*, 1937, xxv, 362
- 13 DODD, K, MINOT, A S, and CASPARIS, H Guanidine as a factor in alimentary intoxication in infants, *Am Jr Dis Child*, 1932, xliii, 1
- 14 MASON, M F, RESNIK, H, MINOT, A S, RAINEY, J, PILCHER, C, and HARRISON, T R Mechanism of experimental uremia, *Arch Int Med*, 1937, lx, 312
- 15 NEALE, R C, and WINTER, H C Identification of active crystalline substance from liver which protects against liver damage due to chloroform or carbon tetrachloride and study of related compounds, *Jr Pharmacol and Exper Therap*, 1938, lxii, 127
- 16 CATTINI, G B Detoxifying action of nicotinic acid, *Dermatologia*, 1940, lxxxix, 83
- 17 ASKENSTEDT, V. W Quantitative determination of indican in urine, *New York Med Jr*, 1912, xcv, 1363
- 18 MARTIN, GUSTAV J, FISHLR, C VIRGINIA, and THOMPSON, MARVIN R Therapeutic and prophylactic detoxication Sulfanilamide, sulfapyridine and sulfathiazole, *Arch Int Med*, 1942, lxxix, 662
- 19 YOUNG, LESLIE Detoxication of carbocyclic compounds, *Physiol Rev*, 1939, xix, 323
- 20 HARROW, B, and SHERWIN, C P Detoxication mechanisms, *Ann Rev Biochem*, 1935, iv, 263
- 21 HEFFTER, A Mechanism of detoxication, *Ergebn d Physiol*, 1905, iv, 184
- 22 ANDROSE, A M, and SHERWIN, C P Detoxication mechanisms, *Ann Rev Biochem*, 1933, ii, 377
- 23 QUICK, A J Detoxication mechanisms, *Ann Rev Biochem*, 1937, vi, 291
- 24 SHERWIN, C P Detoxication of foreign organic compounds in the animal body, *Physiol Rev*, 1922, ii, 258
- 25 GRIFFITH, W H, and LEWIS, H B Studies in the synthesis of hippuric acid in animal organism, *Jr Biol Chem*, 1923, lxxii, 1
- 26 CSOKKA, F A On the administration of various proteins with benzoic acid to a pig, *Jr Biol Chem*, 1924, lxx, 545
- 27 GRIFFITH, W. H Benzoylated amino acids in the animal organism, *Jr. Biol Chem*, 1929, lxxvii, 415

- 28 GRIFFITH, W H Benzoylated amino acids in the animal organism, synthesis of glycine and of hippuric acid in rats, *Jr Biol Chem*, 1930, lxxv, 751
- 29 CATTINI, G B Detoxifying action of nicotinic acid, *Dermatologia*, 1940, lxxvi, 83
- 30 QUICK, A J Conjugation of benzoic acid in man, *Jr Biol Chem*, 1931, xcii, 65
- 31 GRIFFITH, W H, and LEWIS, H B Studies in the synthesis of hippuric acid in animal organism, *Jr Biol Chem*, 1933, lvi, 697
- 32 ANDERHALDEN, E, and WERTHEIMER, E Wird das in dem Zellstoffwechsel einbezogene Eiweiss vor der Überführung in die Stoffwechselendproducte zu Aminosäuren aufgespalten? *Ztschr f physiol Chem*, 1931, cxcviii, 18
- 33 WHITE, A, and LEWIS, H B Metabolism of sulfur, *Jr Biol Chem*, 1932, xcvi, 607.
- 34 STEKOL, J A Metabolism of bromobenzene in growing dogs and mice, maintained on adequate diets, *Proc. Soc. Exper Biol and Med*, 1935, xxxiii, 115
- 35 WHITE, A, and JACKSON, R W Effect of bromobenzene on utilization of cystine and methionine in growing rat, *Jr Biol Chem*, 1935, cxvi, 507
- 36 QUICK, A J The preparation of borneol glucuronic acid and glucuronic acid, *Jr Biol Chem*, 1927, lxxiv, 331
- 37 HEMINGWAY, A, PRYDE, J, and WILLIAMS, R T Biochemistry and physiology of glucuronic acid, *Biochem Jr*, 1934, xxviii, 136
- 38 LIPSCHITZ, W L, and BUEDING, E Mechanism of biological formation of conjugated glucuronic acid, *Jr Biol Chem*, 1939, cxxix, 333
- 39 EPSTEIN, ALEXANDER Vitamin C in desensitization, *Schweiz med Wchnschr*, 1936, lvi, 1087
- 40 LEMKE, H Beeinflussung des anaphylaktischen Shocks der Meerschweinchen durch Vitamin C, *Monatschr f Kinderh*, 1936, lxxvii, 244
- 41 HOCHWALD, A Allergiefragen und Vitamin C, *Zentralbl f inn Med*, 1935, lvi, 769
- 42 HASIMOTO, M, KITAMURA, S, and SUZUKI, S Experimental investigation on action of vitamin C in guinea pig anaphylaxis, *Jr Orient Med*, 1938, xxviii, 20
- 43 YOKOYAMA, S On the influence of vitamin C on anaphylactic shock, *Kitasato Arch Exper Med*, 1940, xvi, 17
- 44 RAFFEL, S, and MADISON, R R The influence of ascorbic acid on anaphylaxis in guinea pigs, *Jr Infect Dis*, 1938, lxiii, 71
- 45 UNGAR, G, and PARROT, J L Recherches sur le choc anaphylactique in vitro, *Compt-rend Soc de biol*, 1936, cxxiii, 676

TULAREMIA; A REPORT OF FOUR CASES WITH UNUSUAL CONTACTS *

By JOSEPH H SHAFFER, M D , F A C P , *Detroit, Michigan*

WHEN we consider tularemia, commonly known as rabbit fever, we are likely to dismiss it with the thought that it is a rather uncommon disease which is far removed from our every day medical experiences. In the past 28 years this disease, first recognized in California, has been found to cause illness in human beings in every state in the union. It is now known that tularemia in addition to affecting the rabbit, is a disease prevalent in 20 or more forms of wildlife in America. This paper calls attention to the occurrence of tularemia in individuals who have not handled rabbits or other game. Three of these patients were infected by domestic cats, and one became ill following the bite of a wood tick.

CASE REPORTS

Case 1 An optometrist, H G, a white male, aged 50, was admitted January 19, 1940, to the medical service of the Henry Ford Hospital. He complained of extreme exhaustion and ease of fatigue on slight exertion. Two weeks before admission he had headaches, muscle soreness and pains, shaking chills followed by fever to 102° F. He had drenching night sweats, and there was a slight, but irritating non-productive cough with tightness in the chest. The above symptoms had been attributed to influenza which was prevalent at that time. Three weeks before admission an itching pustular lesion appeared on the dorsum of the left hand. There were enlarged and tender epitrochlear and axillary lymph nodes in the left arm.

When examined the patient appeared weak and tired. The temperature was 99° F. The chief points of interest were the enlarged left epitrochlear and axillary nodes and the healing pustule on the dorsum of the left hand. The epitrochlear gland measured 9 cm in diameter and was firm and only slightly tender. The lymph nodes in the left axilla were readily palpable and tender. The liver was 5 cm below the costal margin in the right midclavicular line, the edge was firm and sharp, but not tender. The spleen was readily palpable but not tender. Chest roentgenograms were negative for areas of consolidation or enlarged hilar nodes. There was a crusted pustule with an umbilicated center on the dorsum of the left hand. This lesion was 1.5 cm in diameter and was dark red, its appearance suggested a hair-follicle type of infection (figure 1).

There was a mild secondary anemia with slight jaundice. The leukocyte count was 5,350 with 70 per cent polymorphonuclear cells. The blood sedimentation rate was 28 mm in one hour. The Kline exclusion test for syphilis was negative. The patient's blood serum agglutinated *B. tularensis* 1:100. Agglutination for *B. abortus* was negative. When repeated February 2, 1940, five weeks after the onset of the illness, the patient's titer had risen to 1:320.

We were unable to elicit from our patient a history of exposure to rabbits or fowl. Further questioning later revealed that the family cat had limped for several weeks.

* Delivered before the Post-Graduate Conference on Industrial Medicine, American College of Physicians, Detroit, March 29, 1940.

Revised for publication. Received for publication February 17, 1942.

Examination of the cat revealed a healing ulceration on the skin of the left hind leg, but the animal did not appear to be ill. It was the habit of the patient to fondle his pet as it reposed on his lap. The cat's blood serum agglutinated *B. tularensis* 1:360. Agglutination with *B. abortus* was negative.

This patient was given sulfanilamide because of the low grade fever and adenopathy. He received a total of 165 grains over a period of three days when the drug was stopped because of nausea and vomiting. The blood sulfanilamide level had reached 5.9 mg per 100 cc blood, but there was no improvement in the patient's condition during that short period of treatment.

The patient's left epitrochlear lymph node remained large and became progressively more tender and fluctuant. There was also increased redness and heat. In the fifth week the abscess pointed by rupturing through the capsule of the lymph node (figure 2). Simple incision was followed by drainage of several ounces of thick yellow-white



FIG 1 (Case 1) Tularemia infection in man contracted from house-cat. Hair follicle infection on dorsum of left hand two weeks after onset of illness

purulent material. Culture on glucose-cystine-blood agar plate was negative. The incision continued to drain for three weeks, and the patient was not returned to his former state of health until eight months after his initial infection.

Case 2 E. D., a white male physician, aged 26, was bitten by a wood-tick while vacationing in Wyoming, in July 1940. There was marked localized itching, and within a few days an ulcer appeared at the site of the bite. The lesion was several mm deep and the base of the ulcer was studded with elevated, yellow, pin-head sized nodules. The edges of the ulcer were elevated, smooth and rolled (figure 3).

The patient had experienced three weeks of fever, malaise and anorexia with a resultant weight loss of 14 pounds. The right axillary lymph nodes were enlarged and tender, and there was a nodular lymphangitis in the forearm. The leukocyte count was 12,800 with 70 per cent polymorphonuclear cells. The patient's blood serum agglutinated *B. tularensis* 1:40 during the second week of his illness, and 1:160 by the third week. Culture from the ulceration on the forearm was implanted on



FIG 2 (Case 1) Abscessed epitrochlear gland five weeks after onset of illness Simple incision and drainage now indicated



FIG 3 (Case 2) Ulceroglandular tularemia Print from kodachrome picture of skin lesion three weeks following an insect bite The lesion remained an open ulcer for five weeks

cystine-blood-agar; a small gram negative cocco-bacillus was isolated and was indistinguishable morphologically and serologically from *B tularensis**¹

This patient was seen again in the eleventh week of his illness He had regained 12 pounds weight, but continued to tire easily with physical exertion His

* Tests done at the Minnesota Department of Health Laboratories

blood agglutination titer had risen to 1:20,000 with Mulford antigen and 1:1,600 with (H F H) antigen prepared in the hospital laboratory. The ulcer, which had drained for five weeks, was then covered with healthy pink scar tissue. The axillary lymph nodes were barely palpable. His strength had returned and he was able to return to full-time work. A progress blood test January 11, 1941, six months after the onset of illness, disclosed a blood serum agglutination of 1:5,000 with Mulford antigen and 1:2,000 with Michigan Department of Health antigen. He continues now in his usual good health.

Case 3 R. B., a 2-year-old white boy, received a bite on the left cheek from a domestic cat while visiting on his grandparents' farm not far from Detroit, on October 15, 1940. The boy became ill with nausea, vomiting and fever several days after



FIG 4 (Case 3) Infection of the face following the bite of a cat. Abscess continues to drain after three months.

he was bitten. The lymph nodes in the left cervical region became tender and swollen. There was anorexia followed by weight loss, and the boy's color and health in general were poor for several weeks. The wound was cleansed by the mother. When a physician was first consulted about December 15, 1940, a deep abscess of the left face was lanced and purulent material escaped. No culture was taken.

This patient was brought to the Surgical Clinic of the Henry Ford Hospital, January 21, 1941, because of the failure of the lesion on the face to heal. This was three months after the onset of the illness. The boy was not acutely ill. There was an indurated, swollen area just below the left malar prominence. The tooth marks

made by the cat were visible, and at the lower site where the teeth had punctured the skin there was a brown crust of dried serum (figure 4). Moderate pressure caused straw-colored serum to exude from beneath the crust. The serum was sterile when cultured on cystine-blood-agar. The left cervical lymph nodes were enlarged, firm and tender.

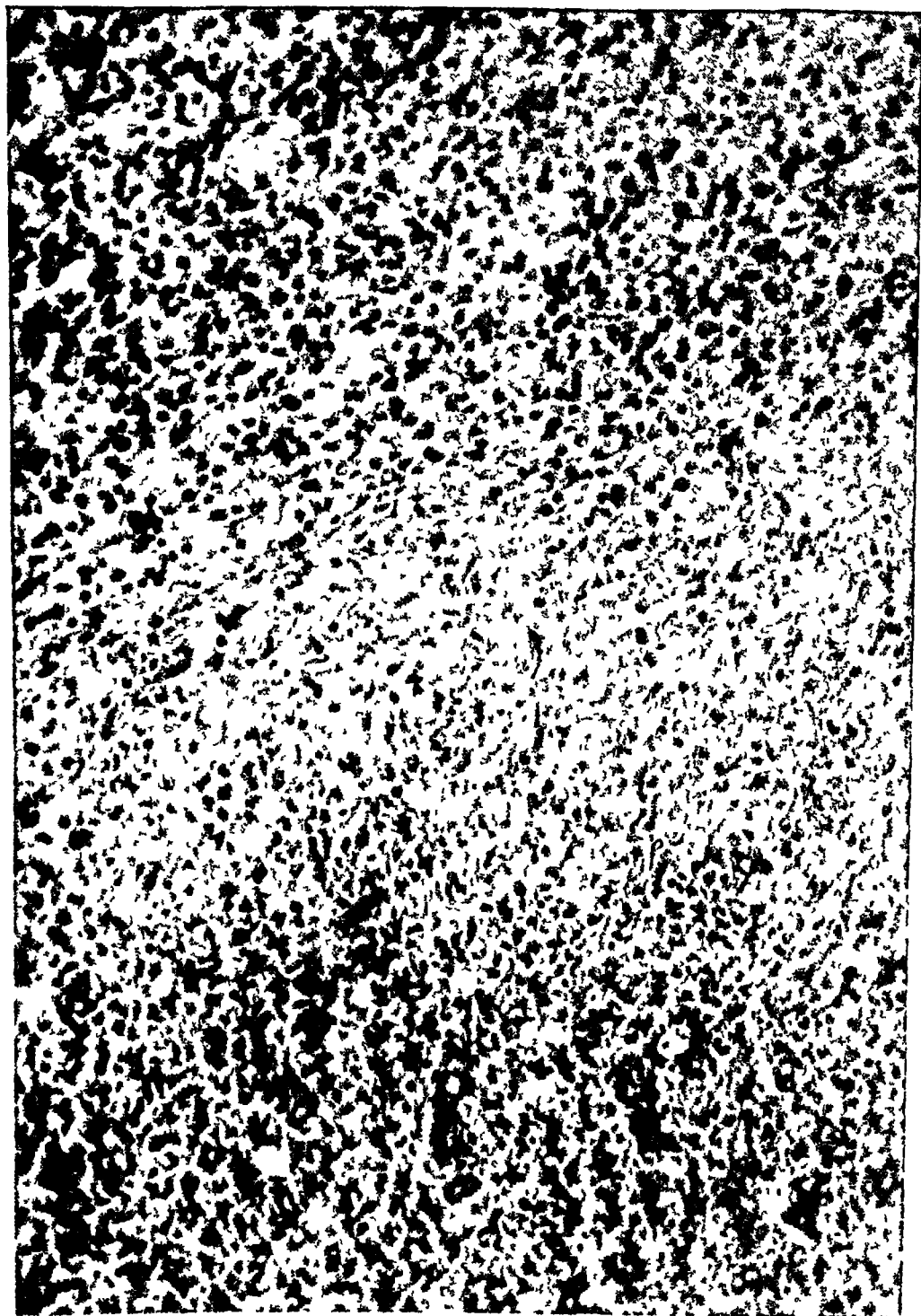


FIG 5 (Case 4) Tularemia. Section of lymph node removed at biopsy.
(Courtesy of Dr. Frank W. Hartman.)

This boy's blood count was normal, but his blood serum agglutinated *B tularensis* 1:200 with Mulford antigen and 1:50 with Michigan State Board of Health antigen.

The cat that bit the boy was brought to the hospital January 28, 1941. It was a huge animal and it did not seem to be ill. There were no skin lesions. The cat's blood agglutinated *B tularensis* 1:50 with Mulford antigen and 1:25 with Michigan State Board of Health antigen. Postmortem examination of the cat revealed no gross or microscopic lesions of tularemia.

Case 4 C F, a white female student, aged 15, had noticed a tender swelling in the left axilla which had appeared insidiously some four to six weeks before. There were no other complaints. Although she was unaware of it, her temperature was elevated to 99.4 degrees F. There was a single tender and enlarged lymph node,

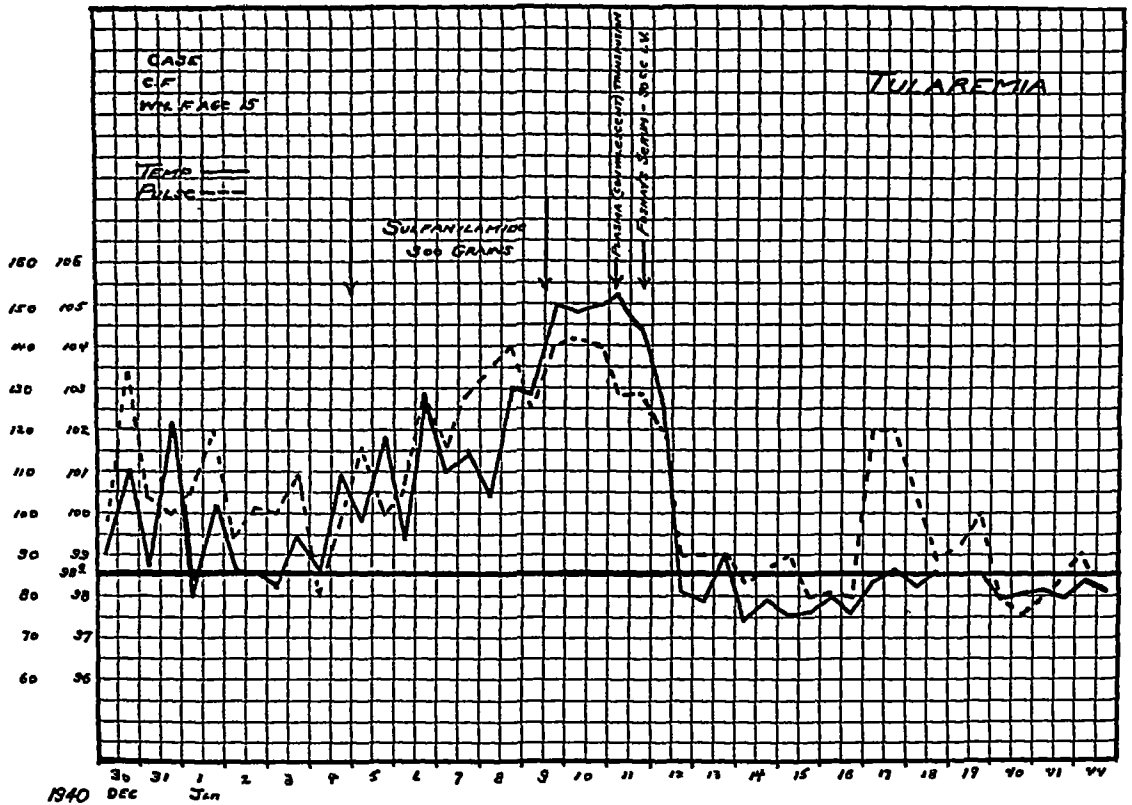


FIG 6 (Case 4) Successful treatment with plasma transfusion from recently recovered tularemia patient, and Foshay's antitularemia serum

approximately 3 cm in diameter, in the anterior portion of the left axilla. There were no other noteworthy features.

The erythrocyte count was 4,860,000 with 13.1 grams (84 per cent) hemoglobin. The leukocyte count was 7,000 with 64 per cent polymorphonuclear cells. Chest roentgenograms revealed some increase in the hilar shadows.

On December 30, 1940, four days after the above examinations, the enlarged lymph node was removed for biopsy. The specimen consisted of two small well-encapsulated lymph nodes, the larger measuring 3 by 1.5 by 1.5 cm. The capsule was thickened and infiltrated with round cells. Scattered throughout the gland were several areas of necrosis which were not caseous in character but contained polymorphonuclear cells. Surrounding the necrotic areas which were oval in shape, were many round cells and some epithelioid cells arranged more or less concentrically. The pathologist's

impression was that the specimen was "lymph-node, chronic granuloma, probably tularemia" (figure 5).

With the above report in mind the patient's history was rechecked. It was learned that the family cat had been irritable and mean and had scratched and bitten members of the patient's family. The patient remembered a slight abrasion on the left index finger where the cat had bitten her some weeks before. Very little concern was caused by the bite inasmuch as it healed without difficulty.

The patient's blood serum agglutinated *B. tularensis* 1:50 with Mulford antigen. There was a foul discharge from the incision in the left axilla. The leukocyte count had risen to 15,950 with 85 per cent polymorphonuclear cells by January 9, 1941. The temperature rose to 105° F. Sulfanilamide had been started on January 4, 1941 and was discontinued on January 9 after approximately 300 grains had been administered without beneficial result. The agglutination titer had risen to 1:100 with Mulford antigen. The temperature reached a peak of 105.2° F. by January 11, 1941, the pulse rate was 140 per minute and the leukocyte count had risen to 16,000.

The patient was given immune serum in the form of a plasma transfusion of 200 c.c. from a recently recovered tularemia patient whose blood serum agglutinated *B. tularensis* 1:5,000 with Mulford antigen. The blood plasma was given at 11:30 a.m. and in the afternoon she was given 30 c.c. of antitularemic goat serum that had just arrived from Dr. Lee Foshay. The goat serum was given in one dose intravenously without immediate reaction. The patient showed striking symptomatic improvement within a few hours. The temperature dropped to 102.6° F. by the next morning, January 12, 1941. By afternoon the temperature and pulse rate had returned to normal and there was no further fever (figure 6). On the fifth day after serum therapy the patient had an urticarial reaction, but she continued to improve generally and left the hospital on the twentieth day. Her blood serum at the time of discharge agglutinated *B. tularensis* 1:1,000 with Mulford antigen.

Two other children from the same family had had contact with the cat. One child had a weak agglutination titer for *B. tularensis*, the other had a negative blood test, although the right epitrochlear lymph nodes were slightly enlarged. Both children remained well.

The family pet cat was brought in for examination. Its blood serum did not agglutinate *B. tularensis*. Gross and microscopic examination of the tissues was negative for tularemia. It was thought that the patient and her younger brother and sister were infected from the contaminated animal which remained free of infection. The family resided in a suburban community where the cat could hunt in nearby fields.

Tularemia in Man Traced to Infected House-Cats In addition to the cases presented in this paper, a review of the literature discloses that Collins,² in 1933, reported ulceroglandular tularemia in a man 14 days following a bite on the index finger by a six month old kitten. The patient's blood serum agglutinated *B. tularensis* 1:1,280, while the cat's blood serum agglutinated the organism 1:80.

Rudesill,³ in 1937, reported tularemia in a woman following the bite of a cat or one of its two nursing kittens. The mother cat had fed on a dead tularemic rabbit. On the thirteenth day the patient's blood serum agglutinated *B. tularensis* 1:80, and on the seventeenth day it was 1:640. The woman recovered after an illness of two months. The mother cat recovered but the two kittens died.

The Public Health Bulletin of April, 1940, reported a total of 13 persons

with tularemia after contact with cats, two having been scratched and 11 having been bitten ⁴

Susceptibility of the Domestic Cat to Infection McCoy and Chapin,⁵ as early as 1911, noted that the domestic cat was susceptible to tularemia. Cats were noticed with buboes from natural infection. They inoculated five cats with a strong emulsion of a 48 hour agar culture, one cat died on the eighth day and four cats developed buboes and ulcerations. The following year the same workers inoculated four cats subcutaneously with large doses of an emulsion from the liver of a guinea pig dead of tularemia. The cats remained well, whereas control guinea pigs died.

Simpson,⁶ in 1929, reviewed experimental work of Wherry, Green, Wade, and Hanson, and Francis pertaining to the susceptibility of the domestic cat to infection with *B. tularensis*. Francis,⁷ in 1924, infected two cats, one by repeated feedings with infected lymph nodes from tularemic guinea pigs, and another by subcutaneous inoculation with a virulent culture of *B. tularensis*. Both cats subsequently died of tularemia. It therefore seems that the domestic cat's susceptibility to *B. tularensis* has, on the basis of experimental work reported to date, been established. The cat has been listed among the mildly susceptible animals.

Reservoir of Infection in the United States Literature on tularemia includes reports of the prevalence of the disease in all sections of the United States. Since 1925 tularemia has been recognized in 10 foreign countries. Investigators have reported tularemia in more than 24 forms of American wildlife such as wild rabbit, coyote, beaver, skunk, raccoon, fox, rat, squirrel, woodchuck, sheep, meadow-mouse, horned owl, pheasant, fish, muskrat, hog, lamb, dog, wood-tick, house-fly, and other insects.

Water-borne infection, presumably from contamination with animals, dead or alive, has been recognized. Positive cultures were obtained on samples of water taken from Montana streams, and tested by the Rocky Mountain Laboratory of the Public Health Service at Hamilton, Montana.⁸

House pets, such as the domestic cat, when kept in rural communities such as was the case in the three instances reported in this paper, may hunt in the fields and thereby become contaminated or infected with *B. tularensis*. Such a possible source for illness in man should not be overlooked.

SUMMARY

1. Four cases of ulceroglandular tularemia in man, occurring without contact with rabbits, have been reported. Three of the patients became ill after contact with pet house cats, and one became ill following the bite of a wood-tick.

2. The susceptibility of the house-cat to infection with *B. tularensis* has been demonstrated experimentally by others. Tularemia in man may follow the bite or scratch of a pet cat, such a source of infection in man should

not be overlooked, especially in suburban and rural communities where the cat may hunt rodents of the field

3 Attention is called to the widespread prevalence of tularemia, not only in rabbits, but in many forms of American wildlife

BIBLIOGRAPHY

- 1 Personal communication to Dr Roy D McClure from O McDANIEL, Director, Minnesota State Health Department
- 2 COLLINS, M W Transmission of tularemia by the domestic cat, New Orleans Med and Surg Jr, 1933, lxxxvi, 105
- 3 RUDESILL, C L Tularemia from the bite of a nursing kitten, Jr Am Med Assoc, 1937, cviii, 2118
- 4 Sources, Symptoms and Prevention of Tularemia, Pub Health Rep, 1940, lv, no 16, 667
- 5 MCCOY, G W, and CHAPIN, C W Domestic animals and plague infection, Jr Infect Dis, 1911, ix, 278
- 6 SIMPSON, W M Tularemia, 1929, Paul B Hoeber, Inc, New York, 46-49
- 7 FRANCIS, E, and LILLIE, R D The pathology of tularemia, National Institute of Health Bull, 1937, no 167, 227
- 8 Tularemia infection (*Bacterium tularensis*) found in streams, Pub Health Rep, 1940, lv, no 6, 227

FACTORS WHICH MAY INFLUENCE SENESCENCE*

By NATHAN SMITH DAVIS III, M D , F A C P , *Chicago, Illinois*

IN any discussion of the factors which may influence senescence, consideration must be given to clinical observations and research and to animal experimentation. Unfortunately there has been relatively little investigation of the problems of involution. Indeed, until recently the subject has attracted little attention. Funds for any such prolonged studies have always been difficult to obtain. As the factors that influence senescence in the experimental animal may not have the same effect on the involuntary processes of man, it will be necessary to use both animal experimentation and clinical research in such studies.

Carcinoma, diabetes mellitus, the arthritides of advancing years, arterial hypertension, atherosclerosis and other "degenerative diseases," and such changes as premature graying of the hair and baldness, are generally believed to be influenced by heredity. It apparently determines not only the particular "degenerative disease" developed by the members of one or more generations of certain families, but also the age at which the disease first makes its appearance. It is, however, often difficult to differentiate between the true hereditary factors, those carried by the genes, and those included under the term "constitution."

"Constitution" is, in part, determined by heredity, and in part by environment. Social, economic and educational factors, familial habits of eating and living, occupation, the climate, the composition of the soil and water and of the food where an individual is born, where he grows up and where he spends his mature years, all have their effects¹. The structure of the teeth of the people who have always lived in Deaf Smith County, Texas, and their resistance to caries, illustrate the influence that soil and water conditions may have on "constitution"². Heredity and environment may both contribute factors which so modify cellular chemistry that they determine the type of involuntary change and the age at which it first appears.

Warkany and Nelson have reported that congenital malformations develop in about one-third of the offspring of female rats bred while on Steenbock and Black's rachitogenic diet No 2956³. They also found that the same female would produce offspring all of which were normal, if 2 per cent of dried pig liver were added to the diet. It requires a frankly deficient diet to produce such gross abnormalities. The nutritional status of the sire at the time of conception was found to have some effect on the offspring, but that of the female was of much greater importance.

It has been conclusively proved that poor and undernourished women are more apt to have spontaneous abortions at almost any stage of pregnancy,

* Read at the St. Paul meeting of the American College of Physicians, April 23, 1942

and to have more stillbirths and offspring who die during the first year of life, than do those who are better nourished⁴ It is also known that the mother who has a chronic or severe acute illness during her pregnancy is apt to have an experience similar to that of malnourished mothers In either case the children are not so strong as those born to healthy well-nourished women Too frequent pregnancies may so weaken the mother that the results are the same⁵ It seems, therefore, that the "constitution" of a human being is influenced by the genes inherited from its parents, by their nutritional status and health at the time of conception, by the nutritional status and health of the mother throughout pregnancy and until supplemental feedings are started, and by environmental factors

The health, nutrition and environment of the human being throughout life may modify the effects of heredity and "constitution" and the development of involutionary changes According to Warthin, the loss of permanent teeth should not commence before the age of 60 is reached⁶ Yet malnutrition during infancy and childhood, plus the diseases that are more prevalent among the poor, who are ill-fed, ill-housed and ill-clad, have caused many young adults of the British Isles and the United States to lose many of their teeth⁷ To be sure, the loss of teeth due to senescence is of a different character from that due to caries, pyorrhea, alveolar abscess, etc However, were it not for these pathological changes in the teeth and gums that are now believed to be caused by improper diet and systemic disease, the teeth would have remained to undergo the regular involutionary changes of aging⁸

The relation of proper nutrition and absence of disease to normal growth and to normal cellular chemistry is well established Reference need only be made to the work of Todd and his collaborators to illustrate the importance of these factors in the proper development of the skeleton and teeth⁹ Their effect on all other tissue cells must be as great McCay has demonstrated in rats that the quality and quantity of the ration is of great importance in determining their longevity¹⁰ He found that a diet that was qualitatively adequate but quantitatively deficient (a diet that retarded growth) greatly prolonged the life of rats It seems logical to suppose that proper nutrition, quantitatively as well as qualitatively, is of at least as much importance in prolonging maturity and postponing involution in the cells of human beings as it is in prolonging the life of the experimental animals

For proper nutrition, a diet is required that contains the vitamins, minerals, amino acids and other elements that are essential to the normal utilization of the amounts of carbohydrates, fats and proteins it contains The relative proportions of the fats, proteins and carbohydrates must also be correct, and the caloric value of the diet such that it satisfies the needs of the particular individual The individual needs during maturity are not just what they were during the growth period or what they will be in old age

The discovery of more effective methods for the prevention, diagnosis and treatment of many of the epidemic bacterial and virus diseases and for

the feeding of infants and children has already reduced the morbidity and mortality rates of infants, children and young adults. As a result, the life expectancy of these age groups has been materially increased¹⁰. There has, however, been but little prolongation of the life expectancy of those who have survived to the fourth and fifth and later decades. Indeed, it is popularly believed that the degenerative diseases are now appearing earlier in life than they formerly did, and that they are causing more deaths in young and mature adults. There is no indisputable evidence as to whether or not there has been a real increase in the number of people who develop involutionary changes prematurely¹². It is certain that little has been learned about the onset, early diagnosis, prevention or treatment of these conditions.

Normal growth requires good health, proper nutrition and absence of disease. Those who have been chronically ill-fed, ill-housed and ill-clad suffer more from disease than do their well-fed, well-housed and well-clad contemporaries who are also apt to live longer lives. Historical evidence shows that this has been true of all races and of all age groups throughout the centuries¹³. Experimental work and clinical investigation have developed a fairly accurate knowledge of the nutritional requirements during the growth period. Almost no work has been undertaken to determine the diet that is optimal during maturity, or the one that is most effective in postponing the involutionary changes of senescence.

The work of Williams and his collaborators on the vitamin content of tissues indicates that the organs studied contain and probably require different amounts of the various vitamin B factors at different ages¹⁴. It seems likely that the content and requirements of the various tissue cells for the other vitamins, for various minerals and for the essential and non-essential amino acids also differ and vary with increasing age. They have also found that feeding hens on a diet enriched with pantothenic acid causes the other "B vitamins" to be altered in their distribution in the chicks hatched from the eggs. This indicates that the different vitamin B factors are not acting entirely independently¹⁵. Furthermore, it has been shown that a relative disproportion of some of these essential nutrients in the diet may be harmful. Certain of them are known to have a stimulating effect on one organ and an inhibitory effect on another¹⁶. Even the vitamins may not always be as harmless as we have been led to believe.

As more is being learned about cellular chemistry, it becomes more and more evident that the amounts of vitamins, minerals and essential amino acids required, depend on the relative and absolute quantities of carbohydrate, fat and protein in the diet. This is to be expected, for these essential elements participate in the formation of the enzymes and hormones required to catalyze the series of chemical reactions that take place in the tissue cells and result in the production of heat and energy. The problems of senescence will undoubtedly be solved when cellular chemistry can explain the involutionary changes that characterize it.

Initial moves toward such solutions for these problems have already been

made DuVigneaud and his co-workers have found that biotin may have a carcinogenic effect¹⁷ Rhoads and others have shown that the vitamin B complex of yeast has an anti-carcinogenic effect in animals that have been fed "butter yellow"¹⁸ What serves as the carcinogenic agent in the development of spontaneous cancer in experimental animals or in man, or in particular organs, has not yet been determined It has been shown that the vitamins in the diet make a difference in cancers other than those induced by "butter yellow"¹⁵ Adequate amounts of methionine and cystine and other unidentified protein factors are necessary for normal liver function¹⁹ Tyrosine or phenylalanine is necessary for normal thyroid, pituitary and adrenal function²⁰ The effects of a deficiency of iron, calcium, phosphorus or iodine in the diet have received a great deal of attention, but little is known about the effects of a deficiency of some of the other minerals that are regularly present in human tissue in minute amounts²¹

Numerous pathologic and clinical observations and a mass of experimental work support the theory propounded by Leary, that atherosclerosis is caused by a disordered cholesterol metabolism²² Winternitz believes that these lesions develop in the scars of subintimal hemorrhages²³ Both may be right The disordered cholesterol metabolism may cause the development of atherosclerosis in those individuals whose diet contains fat in amounts that are not in proportion to its carbohydrate, protein, vitamin, essential amino acid and mineral content, and therefore is not utilized as it should be by the cells of the body The subintimal hemorrhages may develop because of some other type of relative or absolute dietary deficiency In this connection, it must be remembered that in the presence of infection, a diet that has been adequate in all respects may become at least relatively deficient Furthermore, different diets of equal caloric value may be adequate, relatively or absolutely deficient in their content of one or more of the essential elements

There is much evidence that nutrition is of great importance in the treatment of some forms of bone and joint disease that are common in older people²⁴ Proper nutrition has also been found of value in the treatment of heart failure and for the relief of psychoses in aged individuals^{25, 26} This does not mean that the "beriberi heart" or a niacin deficiency psychosis is present in all such cases

The ischemic kidney of Goldblatt has a diminished supply of oxygen and of all other nutriment²⁷ It has been shown that anoxemic renal tissue, *in vitro*, produces pressor amines, as it cannot normally metabolize amino acids²⁸ Such tissue will in time form renin, a protein-like substance that has no pressor effect It is theoretically possible that the series of chemical reactions in the renal cells could be arrested at the same point, and might form the same products when the oxygen content of the blood is normal but the required catalyst lacking Braun-Menendez and his co-workers have shown that renin may be formed by the kidneys of normal dogs that are in shock because of excessive hemorrhage²⁹ This group of Argentinian in-

investigators and the group working with Page in Indianapolis³⁰ agree that the inert renin is formed in the ischemic kidney, enters the blood stream, where it reacts with "hypertensinogen" or "renin activator" to form "hypertensin" or "angiotonin". The two groups do not agree as to the exact rôle of these compounds, as to which are enzymes and which substrate. They agree that the kidney may produce a depressor substance which is called "hypertensinase" by the Argentinians. Infection in the kidney may cause hypertension. The products of bacterial growth may destroy or inactivate catalysts or prevent their formation, and produce the same changes in renal cellular chemistry that are caused by ischemia³¹. It appears, based on the findings in experimental animals, that the bacteria in the intestinal tract may synthesize or destroy vitamins in quantity according to the strains present and the character of the milieu in which they live³². A dietary deficiency that prevented the formation of these catalysts might well have the same effect³³.

Infections such as cholecystitis, tonsillitis and others, both chronic and acute, are known to modify cellular chemistry by inactivating catalysts, by inhibiting their formation or by interfering with the secretion and action of hormones. The unfavorable influence of such infections on diabetes mellitus, coronary heart disease and arthritis, for example, is known to all internists.

Thyroid and other endocrine dyscrasias and the metabolic disturbances of advancing years may be caused by chronic foci of infection or by chronic minimal relative or absolute deficiencies of the vitamins, minerals, amino acids or other essential nutritional elements required for normal cellular activity³⁴. Anoxia may also alter their metabolism. The dysfunctions of the endocrine glands result in an hyposecretion or hypersecretion of normal, or in the formation of abnormal hormones which will alter the chemical reactions in most, if not all of the tissue cells. They may thus initiate or accelerate the involutionary changes of senescence³⁵.

Anoxia, infection and malnutrition may cause similar or even identical alterations in the series of chemical reactions that normally take place in the cells of all tissues and organs. Chronic mild infections, chronic minimal or relative dietary and oxygen deficiencies may have effects all out of proportion to their magnitude. They may instigate changes which become self-perpetuating and steadily increase the resulting functional and organic changes. For example, renin may begin to be formed because of a pyelonephritis. The hypertension formed when it reacts with hypertensinogen causes an ischemia of the kidney. This causes more renin and hypertensin to be formed. After such a vicious circuit has been in operation for some time, it may cause enough anatomic change to perpetuate it even after the primary cause is removed. Such a process will account for the insidious onset, prolonged course and gradually increasing severity of the degenerative diseases.

Many chemical compounds may react with the respiratory enzymes and

inhibit their catalytic action. As a result, some of the remedies used in the treatment of disease may, especially if used indiscriminately, produce serious complications. Cinchophen, amidopyrin, acetanilid, the barbiturates, the thiocyanates and the arsenicals probably are toxic because of some such action. It has been shown that the sulfa drugs are active therapeutically only because they replace a nutritional factor that is essential for the growth of the bacteria against which they are effective⁸⁶. Unless this factor, similar in chemical composition to the sulfa drugs, is present in sufficient amounts, the cellular chemistry of the patient may be similarly affected. French and Weller report that an interstitial myocarditis with eosinophilic cellular infiltration was found in 126 out of 283 necropsies on patients who had received one of the sulfa remedies and in none out of 1423 who had not received any of them⁸⁷. Incidentally, it has been shown that well-nourished individuals tolerate some of these remedies better than do those who are ill-fed. For example, an ascorbic acid deficiency decreases tolerance for the arsenicals⁸⁸. Acute infections may also lessen tolerance for certain drugs.

Deplorable is the popularization of the indiscriminate use of alkalis to neutralize the "acidity" that exists only in the minds of advertisers, and to neutralize normally acid gastric juice. Such modification of peptic digestion can cause an adequate diet to become deficient. Excessive self-medication with alkalis may also cause alkalosis and renal damage⁸⁹. Many of the dusts, gases and chemicals to which employees in industry and urbanites may be exposed, may also modify cellular chemistry. It has been suggested that the carbon monoxide and gasoline fumes inhaled by those riding in or driving motor cars may have some such effects. The ingestion for any length of time of compounds that alter biochemical processes should be expected to promote the involutionary processes that cause the degenerative diseases.

Many of the diets that have been prescribed or advertised for weight reduction are more injurious than the relatively high calorie diets that caused the obesity. Unfortunately, some of the diets of most value in the treatment of certain diseases are of necessity deficient in certain essentials. Patients may continue on these diets for much longer periods than their physician intended, and may develop "sub-clinical" or clinical deficiency states.

McCay's finding that a qualitatively adequate but quantitatively inadequate diet prolongs life in rats would indicate that a diet low in caloric value, which contained the required amounts of all the essential nutrients, should be of value in the prolonging of maturity and in the arresting or postponing of the involutionary changes⁹⁰. His experimental work is confirmed by the finding that the life expectancy of men and women past the age of 40, who are underweight, is greater than that of those who are normal in weight. Both these groups will probably outlive all those who are overweight⁴⁰.

The involutionary biochemical processes which lead to senescence may be influenced by all factors which in any way modify cellular metabolism. Much research and experimentation will be required to determine the exact

nature and relative importance of the factors which interfere with normal cellular chemistry so as to initiate the progressive involutionary changes that result in senescence. The factors that now seem to play an important rôle in the initiation and continuation of these metabolic changes, are (1) Heredity, (2) The health and nutrition of the parents at the time of conception, (3) The health and nutrition of the mother during pregnancy and while nursing the baby; (4) The mild or severe, acute or chronic illnesses that the individual may have at any time during life, (5) Nutrition, its quantity and quality, and its relation to the needs of the particular individual at all periods of life, (6) The environment in which the individual grew up, worked and lived, his occupation, habits and mode of life, (7) The particular gases, dusts, chemical compounds and drugs ingested by accident, while at work or play, and on prescription.

These and other factors affect the rate of growth, the duration of maturity, and the onset and progress of senescent changes. But even under optimal conditions, involution will not be prevented, as it is a normal process in all living cells. Though its ultimate development is inevitable, the positive identification and the elimination, insofar as it is possible, of the factors that are responsible for the premature onset and abnormally rapid development of the involutionary changes of senescence are among the most important problems now before the medical profession.

BIBLIOGRAPHY

- 1 REED, ALFRED C. Environmental medicine, *Science*, 1935, lxxxii, 447-452
- 2 TAYLOR, EDWARD. Preliminary studies on caries immunity in the Deaf Smith County (Texas) area, *Jr Am Dent Assoc.*, 1942, xxix, 438-444
- 3 WARKANY, J., and NELSON, R. C. Congenital malformations on a nutritional basis in rats, *Proc Cent Soc Clin Research*, 1941, xiv, 5
- 4 EBBS, J., ET AL. Nutrition in pregnancy, *Canad Med Assoc. Jr*, 1942, xlv, 1-6
- 5 KLEEGMAN, S. J. Medical and social aspects of birth control, *Jr Lancet*, 1935, lv, 726-732
- 6 WARTHIN, A. S. Old age, the major involution, 1929, Paul B Hoeber, Inc., New York
- 7 ROWNTREE, L. G., ET AL. Health of selective service registrants, *Jr Am Med Assoc.*, 1942, cxviii, 1223-1227
- 8 BECKS, H., and MORGAN, A. F. Tooth decay and pyorrhoëa, *Science Supplement*, 1941, xciv, 9
- 9 TODD, T. WINGATE. Anthropology and growth, *Science*, 1935, lxxx, 259-263
- 10 COWDRY, E. V. The problems of aging, 1939, Williams and Wilkins, Baltimore (Chapter 21, Chemical aspects of aging by McCAY, C. M.)
- 11 Metropolitan Life Insurance Co. New decade opens with record longevity, *Statistical Bulletin*, 1941, xxii, No 6, 4-6
- 12 DUBLIN, L. I., ET AL. The medical problems of old age, 1941, University of Pennsylvania Press, Philadelphia
- 13 SIGERIST, H. Medicine and human welfare, 1941, Yale University Press, New Haven
- 14 WILLIAMS, R. J., ET AL. Studies on the vitamin content of tissues, 1941, The University of Texas, Austin
- 15 WILLIAMS, R. J. Vitamins in the future, *Science*, 1942, xcv, 340-344
- 16 LERMAN, J. Physiology of the thyroid gland, *Jr Am Med Assoc.*, 1941, cxvii, 349-359

- 17 DU VIGNEAUD, V, ET AL The procarcinogenic effect of biotin in butter yellow tumor formation, *Science*, 1942, xcv, 174-176
- 18 RHOADS, C P Physiological aspects of vitamin deficiency, *Proc Inst Med Chicago*, 1940, xiii, 198-205
- 19 RAVDIN, I S L L McArthur Lecture, *Inst Med Chicago*, delivered March 27, 1942
- 20 SCHOENHEIMER, R, and RATNER, S The metabolism of proteins and amino acids, *Ann Rev Biochem*, 1941, x, 197-220
- 21 JEGHERS, H Medical progress nutrition, *New England Jr Med*, 1941, ccxxv, 687-697
- 22 LEARY, T Genesis of atherosclerosis, *Arch Path*, 1941, xxxii, 507-555
- 23 WINTERNITZ, M C, ET AL The biology of atherosclerosis, 1938, Charles C Thomas, Springfield, Illinois
- 24 HENCH, P S, ET AL Rheumatism and arthritis, review of American and English literature for 1940, *ANN INT MED*, 1941, xv, 1002-1108
- 25 PROGER, S Diet and heart failure, *Modern concepts of cardiovascular disease*, 1939, vii, No 12, 1-2
- 26 JOLIFF, N Treatment of neuropsychiatric disorders with vitamins, *Jr Am Med Assoc*, 1941, cxvii, 1496-1500
- 27 GOLDBLATT, H Harvey Lectures, 1937-38, 1939, xxxiii, 237, Williams and Wilkins, Baltimore
- 28 Editorial Amino acid metabolism in the ischemic kidney, *Jr Am Med Assoc*, 1942, cxviii, 899
- 29 BRAUN-MENFONDEZ, E The mechanism of renal hypertension, The Walter W Hamburger Lecture of the *Inst Med of Chicago*, delivered March 3, 1942
- 30 PAGE, I H, ET AL Blood pressure reducing properties of extracts of kidneys in hypertensive patients and animals, *ANN INT MED*, 1941, xv, 347-389
- 31 SCHROFFER, H A, and STEELE, J M Studies on "essential" hypertension, association of hypertension with organic renal disease, *Arch Int Med*, 1941, lxxiii, 261-293
- 32 WILLIAMS, R R Vitamins in the future, *Science*, 1942, xcv, 335-340
- 33 DAVIS, N. S, III The relation of urinary tract pathology to arterial hypertension, *Urol and Cutan Rev*, 1942, xli, 184-187
- 34 STIEGLITZ, E J Geriatric medicine, 1942, W B Saunders and Co, Philadelphia (Chapter 16, Dysfunctions of the thyroid, pituitary and adrenal glands, DAVIS, N S, III)
- 35 COWDRY, E V Problems of aging, 1939, Williams and Wilkins, Baltimore (Chapter 13, The thyroid, pancreatic islets, parathyroids, adrenals, thymus and pituitary, CARISON, A J)
- 36 RUPIN, S D, and GILLFSPIE, J M Mode of action of sulfonamides in vitro, *Lancet*, 1942, i, 36-38
- 37 FRENCH, A J, and WEITER, C V Interstitial myocarditis following clinical and experimental use of sulfonamide drugs, *Am Jr Path*, 1941, xlviii, 109-121
- 38 BRUNDESEN, H N, FARMER, C J, ET AL Detoxifying action of vitamin C (ascorbic acid) in arsenical therapy, ascorbic acid as preventive of reactions of human skin to neoarsphenamine, *Jr Am Med Assoc*, 1941, cxvii, 1692-1695
- 39 STIEGLITZ, L J Alkalis and renal injury, *Arch Int Med*, 1928, xli, 10-15
- 40 Metropolitan Life Insurance Co Girth and death, *Statistical Bull*, 1937, xviii, no 5, 2-5

PERTINENT PROBLEMS OF GERIATRIC MEDICINE *

By EDWARD J STIEGLITZ, M S , M D , F A C P ,
Washington, D C

GERIATRIC medicine is that branch of medical science which treats of the elderly in all their physiologic and pathologic relations. Its problems are not confined to those patients actually senile, for the infirmities and disorders of later years arise insidiously far earlier than their clinical manifestations. Aging, as a process or series of processes, is continuous. It starts at conception and terminates only with death. Aging is a part of living. To arrest aging, therefore, would mean destroying life. Evolution, or growth, and involution, or atrophy, occur simultaneously throughout the life span. Even during fetal life localized atrophies occur, as in the involution of the branchial clefts. Growth of certain cells persists unto the end. These two antagonistic phenomena of aging, occurring asymmetrically at variable rates in different individuals and in different tissues, structures and systems of the same individual at different times, determine the rate and character of senescence. To age is to change.

Age is relative. Aging changes do not conform to rigid calibration on the scale of chronologic time. Biologic age and chronologic age are not necessarily the same. Though they may occasionally coincide, this is the exception rather than the rule. There are many of us physiologically older than our elapsed years and a few younger than our chronologic age. Furthermore, no one individual is of uniform physiologic age throughout. The rate of aging varies with certain cell types and with whole functional units or organs. For example, the cells of the epidermis are relatively short lived and are being replaced constantly, whereas the nerve cells of the cerebral cortex are not replaced as long as the organism survives. The female organs of reproduction go through a relatively rapid involution at about the time of the climacterium, but senescence of other structures is not accelerated at this time. Biologic age, therefore, is a composite sum of the extent of aging of all the constituent structures.

The basic concept that *aging brings change* is the foundation stone not only of young geriatrics, but of its older brother, pediatrics. These two special fields have much in common, not because of the platitudinous definition of senility as a second childhood, but because it is at the beginning and end of the life span that the consequences of aging are most conspicuous. Pediatrics made its greatest advance when it was realized that the child is not merely "the little man," but presented structural, functional, metabolic and immunologic characteristics *peculiar* to the periods of infancy and child-

* Read before 26th Annual Session, American College of Physicians, St Paul, Minnesota, April 23, 1942

hood Senescence, like growth and development, brings insidious and occult changes affecting all the structures and activities of the individual The elderly are not just "old people", they are physically and mentally *different* men and women than in the days of their young maturity These changes are significant in the practice of medicine Normality is not a fixed point but a series of variables which change with age Recognition of these variables is essential in diagnosis The early manifestations of incipient disease are readily confused with the changes of senescence Disease, after all, rarely, if ever, introduces new phenomena, the manifestations arise from exaggerations or distortions of normal reactive mechanisms The symptoms, signs, pathogenesis, course, prognosis and therapy of disease are all altered by the basic biologic changes of aging

How old is old? There can be no unanimity as to just where geriatrics begins any more than there is complete agreement as to where pediatrics ends It is necessary, however, to have some demarcation even if arbitrary Limiting geriatrics to the care of the senile would completely ignore the significant fact that the changes of senescence begin many years earlier Involutional changes, however, are not normally significant before the peak of maturity It is, therefore, pragmatic to consider that the majority of clinical problems peculiar to geriatrics start at about 40 years of age, the approximate meridian of life This does not imply that all of us over forty are decrepit and infirm by reason of senility, but from this age onward occurs the insidious accumulation of involutional phenomena whose later consequences constitute senility The so-called degenerative disorders become conspicuously more frequent at this point in the life span The menace of these chronic and progressive diseases is greatest from 40 to 60 If health can be maintained during these two critical decades, the likelihood of long disability and uselessness from chronic illness after 60 will be reduced immensely Obviously, far more can be accomplished for the aging than for the aged The aged represent the consequences of senescence, the character of involution determines the rate and extent of infirmity in senility Therefore, geriatrics must include care and guidance during the period of senescence An attitude of prophylaxis and preparation during maturity is essential if geriatrics is to prove truly effective

Until recently the biologic problems of aging and geriatrics held largely academic and theoretical interest This is no longer true There is true urgency in the need to know more about aging and to apply more effectively that which is already known¹ In the last 50 years preventive medicine, sanitation and vastly improved pediatrics have raised dramatically the age of our population The major factor has been the saving of young lives by control of infective diseases The increase in average age of the nation was accelerated in the last decade War can but further exacerbate the situation

Only a few figures suffice to reveal the present and impending importance of geriatrics in national health In 1850 the average life expectancy at birth was 40 years In 1900 this had risen to 47 years Since the turn of the cen-

tury the rise has been quickened, in 1930 expectancy was about 60 years for white members of the American population, and in 1940 the average expectancy at birth was 63 years. An increased average expectancy at birth of 16 years (from 47 to 63) in but 40 years elapsed time constitutes such conspicuous handwriting on the wall that no apology for stressing the importance of geriatrics is needed.

In 1900 only 17 per cent of the total population of the United States were 45 years old or more. In 1940, 26.5 per cent exceeded 45 years of age. Conservative projection results in the estimate that in 1980 more than 40 per cent of the population will be over 45.² The median age of our population increased from 26.4 years in 1930 to 28.9 years in 1940, a rise of two and one-half years within a single decade. The numerical increase in the elderly is far greater than most of us realize. The total population of this country increased 72 per cent in the 10 years from 1930 to 1940, whereas those 65 years or older increased 35 per cent in the same interval. There are now approximately nine million persons of 65 or more in the United States.²

The implications of these facts are too vast to be considered here. The situation is without precedent. In the past, conspicuous shifts in population structure have arisen as results of destructive forces such as wars, famines and pestilence, but always the changes were in the direction of relative increase in youth. The less fit failed to survive. Today we are faced with the enhanced survival of less vigorous youths because of the protection of medical science and the lessened rigors of modern civilization. The apparent boon of increased longevity may become a curse. Longevity without health is more than individual or personal tragedy. In the aggregate it becomes a dangerous economic burden upon the nation. The social burden of chronic physical and mental illness among senescents is already immense.³ It is steadily increasing.⁴ We can ill afford additional loads now. Contrariwise, however, longevity with health, prolonged usefulness and productivity can be made into an incalculably valuable asset, for there exists in the elderly an immense, largely unutilized and little appreciated reservoir of accomplishment. Upon the balance sheet of our human resources chronic illness with long and progressive disability and the failure of society to employ many functionally capable among the elderly must be recorded as liabilities. Offsetting these are the potential assets of wisdom, judgment, accumulated skills and the desire to serve characteristic of later maturity. These are available, if health is maintained. The effectiveness of geriatric medicine, particularly in its preventive aspects, will determine the final balance. This heavy responsibility rests squarely upon the medical profession, though the majority of its members are unaware of it.

Many misinterpret the objectives of geriatrics as being limited to the prolongation of life and the relief of suffering. Such is a most inadequate concept. Geriatrics can and should aim far further than this. The normal life span of any species has definite biologically determined limits. There

is no desire to arrest aging. To do so would mean terminating life. Rejuvenation is a myth begotten of wishful thinking. Proper medical guidance, however, can prevent, retard or control disease so that disability may be postponed until true senility causes infirmity and thus add to the health, vigor and usefulness of the later years. The primary objective of geriatrics has been most brilliantly epitomized by Piersol and Bortz⁵: "The society which fosters research to save human life cannot escape responsibility for the life thus extended. It is for science not only to add years to life, but more important, to add life to the years."

How may this desirable objective be attained or approached? All manner of therapeutic measures are needed, it is impossible to answer in full at this time⁶. But if we classify therapeutics by its objectives rather than its methods, the issues are simplified. Well-known and conventional are therapy for prophylaxis, for cure, and to palliate symptoms. The effectiveness of prophylactic treatment, however, is conditioned by the precision and completeness of knowledge concerning the etiology of a disorder. Herein geriatrics is severely handicapped in contrast with pediatrics, for our understanding of the etiologic factors of most of the disorders of later years is nebulously vague and incomplete. The same basic obstacle effects curative therapy, for cure of disease is predicated upon eradication of the causes thereof. Furthermore, cure is obstructed by the diminution of the capacity of the senescent organism to repair itself after injury⁶. Palliative therapy seeks merely to conceal distressing symptoms in otherwise hopeless situations. It would be discouraging indeed if palliative treatment were the only type from which geriatric medicine could hope to get results.

A less clearly appreciated objective is control. Control is not cure, nor is it mere palliation. Control is the type of therapy applied in diabetes mellitus, hypertensive arterial disease, arteriosclerosis, myxedema, pernicious anemia, gout and the climacterium. The controlled diabetic still has diabetes, but he is physiologically well. Frequently, but not invariably, control of chronic and progressive disease is accomplished by replacement therapy. It is curious that the adjective "controlative" is not in the dictionary. It should be. Its meaning is surely clear to all. "Controlative" therapy seeks not only to reestablish homeostasis disturbed by disease, but also to *retard progression*. Senescence per se, and most of the chronic and progressive disorders of later years, are not amenable to cure. They are, however, amenable to control and retardation. This is the form of therapy most appropriate to the majority of the problems of geriatric medicine.

One more therapeutic objective must be considered: *constructive therapy*. There has been little of this applied to adults, but pediatricians have taken apparently well babies and made them healthier by scientific feeding and meticulous attention to hygiene and immunity. These healthier children become healthier adults. Similarly geriatrics has the opportunity to modify and retard the detrimental consequences of senescence. Health is relative, never absolute. There is always room for improvement. Treatment of

disease is a "reconstructive" function. It is suggested that treatment of the apparently well, to raise health closer to an optimum, be called "constructive therapy." Not only does this newly applied term adequately define the objective, but it may also serve another useful purpose in diminishing the resistance of men and women to what has been called loosely "preventive medicine." To the average mind prevention implies prohibition and irksome restrictions to avoid something which, with luck, may be escaped anyway. Prevention has a negative connotation. Construction is positive. Constructing health rather than merely preventing illness follows the ancient axiom of war. Attack is the best defense.

The potentialities of constructive and "controlative" therapy for adults are immense. Conscientious application of existing knowledge in such fields as nutrition, endocrinology, hematology and psychiatry can do much to increase well being during senescence. Such guidance, however, *must be applied individually*. The wholesale methods of public health are decidedly inadequate for older age groups. The method of the wholesale approach has been directed toward keeping sources of injury away from the individual. No improvement in the intrinsic vigor, resistance and endurance of the individual can be expected from these methods. Sanitation, quarantine and mass immunization have brought about a brilliant reduction in morbidity and mortality from infective diseases. Thus the major benefit has been with the young. These measures have no effect upon the incidence, disability and mortality from degenerative disorders such as cardiovascular disease, arthritis, diabetes mellitus, anemia, gout or cancer. These latter major sources of illness in later years are endogenous. Protection from external menace will not prevent them.

Constructive or preventive medicine for adults must deal with people individually. With age comes increasing divergence among individuals. Individuality may be defined as the composite of the physical, mental and functional attributes congenitally inherited and modified by the innumerable intoxications, fatigues, infections, psychic and physical traumata which constitute the vicissitudes of existence. It is these latter modifying factors which vary markedly. No two persons live identical lives.

The keystone of the arch of geriatric medicine is the *periodic health inventory*. The bridge heads are thoroughness and individualization in diagnosis and, especially, management. Such inventories should be more than merely examinations to rule out florid disease. Health evaluation must include clinical studies to measure functional reserve capacities. Early detection of depreciation of functional capacities permits of wise counsel to protect the senescing or injured structure at a time when rest, proper nutrition, correction of anemia, and other items may accomplish the most in prolonging relative health. The value of such periodic audits depends upon the quality of the advice. A complete diagnostic study merely recorded on the clinical record does the patient little good. Diagnosis exists for the purpose

of treatment, whether it be reconstructive therapy for disease or constructive therapy to make health more nearly optimal

There are many obstacles to the accomplishment of these objectives. They are serious, but not insurmountable. Expense is the first difficulty. Health mensuration requires time for functional study and the highest type of diagnostic acumen. Secondly, clinicians are sadly handicapped by lack of clinical methods for measuring many functional reserves and also by inadequate data as to what constitutes normality in relation to age. There is urgent need for research along both these lines. The criteria of health vary with age. Thirdly, there has been an unfortunate lack of appreciation of the potentialities of preventive geriatrics⁷ on the part of physicians. And last, but not least, is the obstacle arising from the fact that the initiative for such constructive guidance must be taken by the patient. Perhaps a major reason why public health has been so effective is that its methods demanded no effort on the part of the beneficiaries of the blessings of sanitation. The older person seeking to maintain health *must* exert himself on his own behalf. There is an immense inertia against prophylaxis of any type. The benefits of prevention are demonstrable only statistically and statistics have little emotional appeal. However, constantly reiterated educational efforts can convert this paralyzing inertia into creative momentum. Pediatrics is having less and less difficulty in applying the principles of constructive therapy.

At this time of stress, when greed and hate threaten the very existence of our culture and military activity takes rightful precedence over all else, it may seem incongruous to emphasize the importance of geriatrics and to urge that more attention be paid to the health of those past the meridian. But defense, like therapeutics, is more than heroic attack upon exogenous menaces, no matter how vital that may be. Defense must consider the internal milieu of the body politic as medicine is attentive to the homeostatic mechanisms of the sick organism. The equilibrium of the nation is disturbed by the shifting balance of our population. This shift may prove wondrously advantageous if increased longevity is paralleled by health and productiveness. It may become disastrous if the chronic, progressive and disabling disorders of later maturity are not controlled. Not infrequently the most precarious period of an illness is *after* the crisis. We must see ahead and become better prepared to cope with the problems of senescence through research and more conscientious clinical application of existing knowledge.

Even in the immediate present geriatrics is urgently significant. Industry is becoming aware of the increasing importance of the older worker.⁸ Experienced, skilled men are needed, young men are going into military service. There is great need for objective data concerning such problems as changes in capacities which come with aging, relation of age to fatigue, the effects of specific occupations in exacerbating chronic disease, criteria of physical and mental fitness in later years, and many more.

Furthermore, the leaders in all fields of endeavor are older men. Wisdom is conditioned by experience, which is a factor of time, or age. Aging does *not create* critical judgment, but fosters its growth when intelligence exists in youth. The young fool will become the old fool, should he live long enough, but the bright lad should become a usefully wise old man. Aging fixes and intensifies character. Understanding thinkers become increasingly tolerant and wise, the sanctimonious become opinionated bigots. The decisions of older men guide the national destiny. Special knowledge, trained judgment, and experience make many elderly men almost irreplaceable. The tragedy of premature disability, death or forced retirement of a wise leader is not a personal one, it is a loss to the nation of judgment which can be replaced only by years of experience. The added stresses of the present emergency are added menaces to health. The conservation of the health and effectiveness of older men in posts of grave responsibility is a major obligation of medical science, an obligation not primarily to the individuals themselves, but to the Nation and our culture.

Every privilege entails equivalent responsibility. Failure to conform to this law of nature has caused the decline and fall of many cultures. It is so easy for the individual to accept privilege that before long it is taken for granted as an inalienable right. We have no right to freedom unless we struggle for it, we have no right to health without effort on our part. The privilege of longevity entails the obligation of endeavor to prevent long and premature disability. Individual effort to maintain health and continued usefulness into late senescence is a duty to the community. As the youth prepares to become an adult, so should the adult prepare for senescence and senility. The time to start application of constructive medicine in late maturity is *now*.

BIBLIOGRAPHY

- 1 STIEGLITZ, E. J. The urgency of gerontology, News Edition, Am Chem Soc, 1941, xix, 1147
- 2 Bureau of the Census, U. S. Department of Commerce, "United States Life Tables, 1930-1939 (Preliminary)," July 21, 1941, "Composition of the Population by Age, Sex, and Color, United States (Preliminary), 1940," Series P-5, No. 1, Jan. 30, 1941, "Estimated Future Population, by Age and Sex 1945 to 1980, the United States," Series P-3, July 23, 1941
- 3 BOAS, E. P. The unseen plague chronic illness, 1941, J. J. Augusten, New York.
- 4 LANDIS, C., and PAGE, J. D. Modern society and mental disease, 1938, Farrar and Rinehart, New York.
- 5 PIERSON, G. M., and BORTZ, E. L. The aging process. A medical-social problem, ANN INT MED, 1939, xii, 964
- 6 STIEGLITZ, E. J. Geriatric medicine, 1943, W. B. Saunders Co., Philadelphia
- 7 STIEGLITZ, E. J. Potentialities of preventive geriatrics, New England Med. Jr., 1941, ccxxv, 247
- 8 STIEGLITZ, E. J. Aging as an industrial health problem, Jr. Am Med Assoc., 1941, cxvi, 1383. Aging as a problem of industrial health, South Med and Surg, 1941, ciii, 546

CASE REPORTS

ACUTE THROMBOCYTOPENIC PURPURA HEMORRHAGICA WITH LYMPHOCYTOSIS; REPORT OF A CASE*

By MORRIS TAGER, M D, and KALMEN A KLINGHOFFER, M D,
New Haven, Connecticut

IN 1936, Minot presented three cases of acute thrombocytopenic purpura hemorrhagica with lymphocytosis,¹ and three related cases of intermittent purpura associated with menstruation. No further cases of this nature have been reported, although a fourth one, unassociated with menstruation, has been seen by Minot² since 1936. In view of the difficulty of early diagnosis and the importance of prompt recognition of this dyscrasia, it was deemed of interest to present the following case.

CASE REPORT

The patient, a 20-year-old, single, white, female law student, was admitted to the New Haven Hospital on October 6, 1938. She had been in excellent health until 24 hours before hospitalization, when she first noted several small red spots on her face, tongue, and buccal mucosae, her attention having been called to the latter by slight gingival bleeding. These manifestations were not associated with any local or general discomfort, although there had been a sensation of some blood trickling from time to time in the nasopharynx. During the night, however, she became dizzy, apprehensive, and experienced several chills, without any actual rigor. She attempted to rise to seek aid, lost consciousness momentarily, and fell, bruising her right elbow. She recalled nothing further except that she perspired freely during the rest of the night. On the morning of October 6 she noted many new purpuric lesions scattered over her body, especially on the feet. There was no headache nor other pain, no obvious bleeding from the gastrointestinal or genitourinary tract. The last menstrual period had occurred some two weeks prior to this acute episode and was in no way remarkable. There was no history of any recent acute infection, no known exposure to chemicals, no intake of drugs other than rarely an aspirin tablet, and no dietary deficiency. The patient had no known contact with anyone presenting similar lesions. The past history was negative for any hemorrhagic phenomena and was otherwise not remarkable, except for some evidence pointing to allergy in that she had had mild symptoms of hay fever for five years and an isolated instance of strawberry sensitivity some 10 years previously. There was no family history of blood dyscrasia, and the remainder of the history was non-contributory.

Physical examination upon admission revealed a well developed and nourished girl of 20, cooperative and alert, and not appearing chronically or even acutely ill. There was no pallor nor icterus. The temperature was 101° F (rectally), pulse 80, respirations 20, and the blood pressure 120 mm Hg systolic and 80 mm diastolic. Complete physical examination, excepting the purpura, showed nothing remarkable.

* Received for publication March 4, 1941.

From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital, New Haven, Conn.

Worthy of special note was the absence of splenomegaly, lymphadenopathy, and evidence of significant internal bleeding. Scattered over the face, palate, and lower extremities were numerous petechiae of varying size. Except for a large ecchymosis of the right elbow, the site of injury during the preceding night, the upper extremities and trunk were largely spared. On the lips, tongue, and gums were purplish-red lesions with elevated borders and several millimeters in diameter, presumably secondary to the extravasation of blood. The gums were otherwise not spongy or swollen. There were no splinter hemorrhages under the finger nails.

Laboratory Findings Although the urine was clear on admission, it became grossly bloody within 12 hours, but reverted to normal by the eighth hospital day. Similarly, the stools which became grossly bloody 48 hours after admission, and subsequently became tarry, were free of gross and microscopic blood by the eighth hospital day.

The non-protein nitrogen was 24 mg per cent, icteric index 7, Kahn reaction negative. Blood culture showed no growth. Stereoscopic roentgenogram of the chest revealed no abnormality.

On the day of admission, October 6, 1938, the coagulation time in three successive tubes was 15, 18 and 20 minutes respectively (test tube method), and the clot failed to retract in 24 hours. The bleeding time (Duke's method) was over 24 minutes. On October 17, 1938, the eleventh hospital day, although the coagulation time was normal, the clot still failed to retract in 24 hours, and the bleeding time was 10 minutes. By October 26, 1938, no abnormalities were detectable in any of these tests.

On admission the capillary fragility test, performed by maintaining the blood pressure cuff for five minutes at 110 mm of mercury, was strongly positive, over 100 petechiae being present in a 2½ cm circle.

The sheep cell agglutinations were as follows:

October 6, 1938—1	32 absorbed by guinea pig kidney
October 17, 1938—1	16
December 24, 1938—1	2

In table 1 selected blood counts are presented with the differentials limited to the cells of particular interest for this case. It will be noted that the admission red blood count and Sahli hemoglobin were within normal limits, but dropped to a low of 3.1 million and 55 per cent hemoglobin during the period of severe blood loss of the first week of hospitalization. A few normoblasts were noted during this period, but they were not in evidence subsequently. The red cells showed no other abnormality on smear nor when the various cell indices were calculated. The red cell counts and hemoglobin values were normal by the ninth hospital day.

The total white cell count was characterized by a moderate elevation during the first four days, followed by normal subsequent values. The neutropenia on admission was succeeded by a gradual rise in the granulocyte series, associated with a shift to the left persisting from the eighth to the thirtieth day of illness. Of the "normal" lymphocytes, there was a higher proportion of large cells than is ordinarily found. The eosinophiles, basophiles, and monocytes were within normal limits, or unnoted.

The distinctively abnormal features consisted in the presence of "pathological cells" and the striking reduction of platelets.

The "pathological cells" were largely atypical, young mononuclear cells of varying sizes, shapes, and staining reactions, with predominantly non-granular, well-staining blue cytoplasm and leptochromatic nuclei. Some were not unlike the cells encountered in infectious mononucleosis, a few were indistinguishable from blasts. These cells reached a peak of 68 per cent of the total on the seventh hospital day, and were occasionally encountered as late as 70 days after the onset of the illness.

Platelets were completely absent from the smears during the first four days, but appeared, though greatly diminished, by the fifth day. The counts, listed in table 1, demonstrate the persisting depression of platelets for some three weeks, following which a return to normal took place

Clinical Course The patient's temperature fluctuated between 99° and 101° F during the first week, but was not elevated thereafter except for an occasional rise to 99.6° F. She was placed on strict bed rest, and in view of the normal admission red blood cell count and hemoglobin level and the presumptive diagnosis of acute leukemia, transfusion was withheld during the first 24 hours. However, with the progression of the purpura, notably an increase in cutaneous petechiae, gingival bleeding, the appearance of hematuria and melena, and the consequent development of anemia, a series of small transfusions (table 1) was administered. The clinical course was rapidly

TABLE I

Illness Day	R B C	Hgb % Sahli	Total W B C	Pmn % Seg	Pmn % Non-Seg	Lymph Normal	Pathol Cells	Platelets	Transfusions cc
1									
2*	4.5	86	14,880	6	4	55	35	0†	
3	4.7	88	11,600	6	2	24	66	0†	250
4								+‡	250
5	4.6	78	13,750	14	7	13	66		
6									125
7	3.3	59	6,900	19	9	12	60		300
8	3.1	55	5,700	18	6	8	68		300
9	3.5	72	7,500	16	16	28	40		300
10	4.0	81	7,550	15	8	32	44		
12								15,000	
13	4.3	82	5,800	13	18	48	15		
16	4.0	75	5,550	15	20	48	17		
19								43,000	
22	4.0	82	5,650	21	21	42	12		
23								75,000	
27†	4.2	82	6,600	23	27	43	4	185,000	
31	4.0	75	8,100	37	15	40	2	300,000	
38								700,000	
71	4.1	81	6,600	44	10	42	1		
99	3.9	81	7,200	44	5	38	0		
178	3.9	78	6,200	41	4	44	0		
255	4.2	81	9,400	40	3	52			

* First hospital day
† Day of discharge from hospital
‡ Smear observations

favorable, with the hematuria and melena no longer present by the eighth hospital day, and all cutaneous manifestations of purpura absent by the fourteenth day. No new physical findings appeared and the patient was discharged on October 31, 1938, to convalesce further at home. During the following eight months she returned for frequent hematological and physical examinations. Except for the persistence of a few pathological cells until the seventieth day, nothing significantly abnormal was encountered clinically or hematologically. To the present time, some two and one-half years after the acute episode, the patient has remained completely well.

DISCUSSION

The diagnosis on admission to the hospital presented considerable difficulty. It was the consensus of all observers that acute leukemia was most likely, the

coexistence of a strikingly pathological blood smear and profound thrombopenia with purpura hemorrhagica making this diagnosis a virtual certainty. However, it was equally evident that the nature of the abnormal cells was obscure, and that they were difficult to classify on the basis of present knowledge of cell morphology. The futility of basing a definitive diagnosis on the morphology of the cells alone becomes apparent from the conflicting opinions of several well qualified authorities in various centers to whom the smears were submitted. Indeed, acute myelogenous, lymphatic, and monocytic leukemias were all suggested, the latter on the basis of supravital studies. A later opinion, which had the advantage of knowledge of the favorable progress of the case, was acute toxic injury to the hematopoietic tissues.

The appearance of some of the cells also raised the possibility of infectious mononucleosis. Thrombocytopenic purpura, however, is extremely rare in this disease, and the total absence of the usual clinical features, as well as significant elevation of sheep cell agglutinins, eliminated it as a diagnostic possibility. Although the absence of leukocytosis, lymphadenopathy, and splenomegaly is not incompatible with the diagnosis of acute leukemia, the absence of anemia in the presence of well marked thrombocytopenic purpura is most unusual, and might well have raised some doubts as to the correctness of such an interpretation.

Dr William Dameshek, who was among those consulted, suggested that the present case might fall in the category described by Minot. Although admitting that statistically it was all but a 100 per cent chance that the occurrence of a very marked lymphatic reaction in association with the absence of blood platelets pointed to acute leukemia, he was impressed by the paucity of true blasts, and interpreted the morphologically dominant cell as representing abnormal lymphocytes of varying sizes, shapes, and staining reactions.

It is evident that this view is probably correct. This case shares with Minot's first three cases the diagnostic features of sudden appearance of hemorrhagic phenomena, profound thrombocytopenia, abnormal lymphocytosis, absence of initial anemia, favorable response to transfusion, and ultimate recovery.

The prognosis of this dyscrasia, unassociated with menstruation, is excellent. Although Minot's third case, that of the 10 year old girl, has been lost track of, he has been able to follow his first two cases, both males, for totals of six and nine years respectively, without any evidence of recurrence.² The present case has remained entirely well during the past two and one-half years.

Since all reported cases have received blood transfusions, it is obviously impossible to be entirely certain whether the untreated patient suffering from this disease might not recover spontaneously without such therapy. The risks of irreversible damage to vital organs in the course of a virtually total thrombocytopenia are, however, too well known to allow a patient to go without benefit of such therapy. The danger to the patient of a failure to recognize this dyscrasia, therefore, lies chiefly in regarding it either as a case of acute leukemia, in which, in the absence of anemia, transfusions might be considered elective rather than imperative, or as a case of idiopathic thrombocytopenic purpura hemorrhagica requiring splenectomy.

No clues are at hand as to the etiology or pathogenesis of this disease. Detailed inquiry as to any possible infectious, allergic, or chemical antecedents, failed to bring to light any likely incitant.

SUMMARY

A case of acute thrombocytopenic purpura hemorrhagica with abnormal lymphocytosis occurring in a 20 year old white female is presented. It was characterized by the sudden appearance of hemorrhagic phenomena in the absence of initial anemia, profound thrombocytopenia, "abnormal" lymphocytosis, favorable clinical course following blood transfusions, and no recurrences during the follow-up period of two and one-half years.

BIBLIOGRAPHY

- 1 MINOT, G R. Purpura hemorrhagica with lymphocytosis, an acute type and an intermittent menstrual type, *Am Jr Med Sci*, 1936, cxcii, 445
- 2 MINOT, G R. Personal communication

**STUDIES ON THE EFFECT OF MASSIVE QUANTITIES OF
SODIUM BICARBONATE ON THE ACID BASE
EQUILIBRIUM AND ON RENAL FUNCTION**

REPORT OF A CASE WITH REMARKABLE TOLERANCE*

By JOSEPH B KIRSNER, M D, Ph D, and WALTER LINCOLN PALMER,
M D, Ph D, F A C P, *Chicago, Illinois*

INTRODUCTION

ALTHOUGH considerable emphasis has been placed on the development of alkalosis during the alkali treatment of peptic ulcer, this complication does not occur in most patients so treated. Recent studies¹ have indicated that therapy may be continued for many years without significant alteration either in the acid base balance or in renal function. Berger,² Jeghers and Lerner,³ and others occasionally have observed patients in whom the prolonged use of large quantities of sodium bicarbonate and calcium carbonate caused no apparent untoward effects. This remarkable tolerance to alkalis is particularly well illustrated by the following case in which the ingestion of the enormous quantity of 32,000 grams of sodium bicarbonate in 20 months produced only minimal changes in the acid base equilibrium and no demonstrable decrease in the urea clearance.

CASE REPORT

E. L. R., a 23-year-old unemployed shipping clerk, had experienced ulcer distress for five years, during which time hospitalization had been required on two occasions because of massive hemorrhage. Alkalosis was said to have been present on one occasion as a result of the excessive ingestion of alkali following the appearance of tarry stools. This happened one year before his admission to the University clinics. Physical examination at the time of admission was negative except for localized tenderness in the epigastrium. Roentgen studies disclosed a stenosing duodenal ulcer with a

* Received for publication June 21, 1941

From the Frank Billings Medical Clinic, the Department of Medicine, University of Chicago

crater measuring 15 mm in diameter. The patient was observed in the hospital for 11 months (September 3, 1938, to August 1, 1939) and subsequently in the University clinics until November 13, 1940, a total period of 27 months. The method of study was as follows:

No alkali was administered for several days. Control determinations were made of the serum CO_2 , pH and chloride, and of the blood urea nitrogen.⁴ Renal function was estimated by several urine concentration tests and by the urea clearance test of Van Slyke.⁵ These studies were repeated at least twice each week during the period of hospitalization and at less frequent intervals in the Out-Patient Department. Occasional measurements were made also of the total base⁶ in the serum. The fluid intake and output were recorded daily for nine months of the hospital stay. The daily protein content of the diet was estimated during the entire study because a low protein intake may be accompanied by a depression of the urea clearance despite normal renal function.

Diet—Protein Intake The basic diet in the hospital consisted of 90 c.c. of equal parts of milk and cream taken at hourly intervals from 7 a.m. to 7 p.m. Feedings consisting of soft bland foods were added gradually so that after four weeks the patient received a modified three meal ulcer diet with hourly milk and cream. After discharge from the hospital the quantity of milk and cream was decreased and the three

TABLE I

Month Year	Avg Daily Fluid Intake	Avg Daily Urinary Output	Gastric Aspiration	
			Avg Daily Amount	No of Days Aspirated
Nov 1938	3,478 c.c.	2,458 c.c.	388 c.c.	10
Dec "	3,253	2,539	347	27
Jan 1939	3,718	2,923	282	22
Feb "	5,011	3,936	228	28
Mar "	4,951	3,378	188	29
Apr "	4,588	3,377	143	25
May "	4,326	2,650		
June "	4,422	2,780		
July "	3,446	1,792		

meal program enlarged. The protein intake, although somewhat reduced during the initial four to six weeks, was consistently above basal requirements, averaging 55 grams daily for the first month (September 3 to 30, 1938), 77 grams during the second month (October 1 to 31, 1938), and 102 grams daily between November 1 and 30, 1938. The protein intake during December (December 1 to 31, 1938) averaged 88 grams per day and was maintained at approximately this level for the remainder of the study.

Fluid Balance The fluid intake and output were measured daily between November, 1938, and August, 1939, and are recorded as averages per day during each month in table 1. The large quantities of alkali administered precluded occasional efforts to reduce the 24 hour fluid intake below 3000 c.c. The gastric contents were aspirated nightly for a period of six months (November, 1938, to April, 1939). The quantities removed varied widely, ranging from 30 to 950 c.c., the average daily amounts withdrawn are noted in table 1. It will be observed that the volume of aspirate per day gradually decreased from an average of 388 c.c. in November, 1938, to 143 c.c. in April, 1939.

Alkali Therapy This was begun several days after admission to the hospital and continued for 20 months, the intake per month is shown in the chart. Between September 6, 1938 and September 30, 1938, the patient received 135 grams of sodium bicarbonate, 219 grams of calcium carbonate and 352 c.c. of aluminum hydroxide

During October 1938, 48 c c of aluminum hydroxide, 302 grams of calcium carbonate, and 830 grams of sodium bicarbonate were given. Massive quantities of sodium bicarbonate were administered between November 1, 1938, and April 22, 1940. The daily intake averaged 90 grams for the eight month period between November 1, 1938, and August 1, 1939. The quantity of alkali was then gradually reduced to 60 grams daily between August 1, 1939, and December 1, 1939, and for the five month period between December 1, 1939, and April 22, 1940, averaged approximately 30 grams per

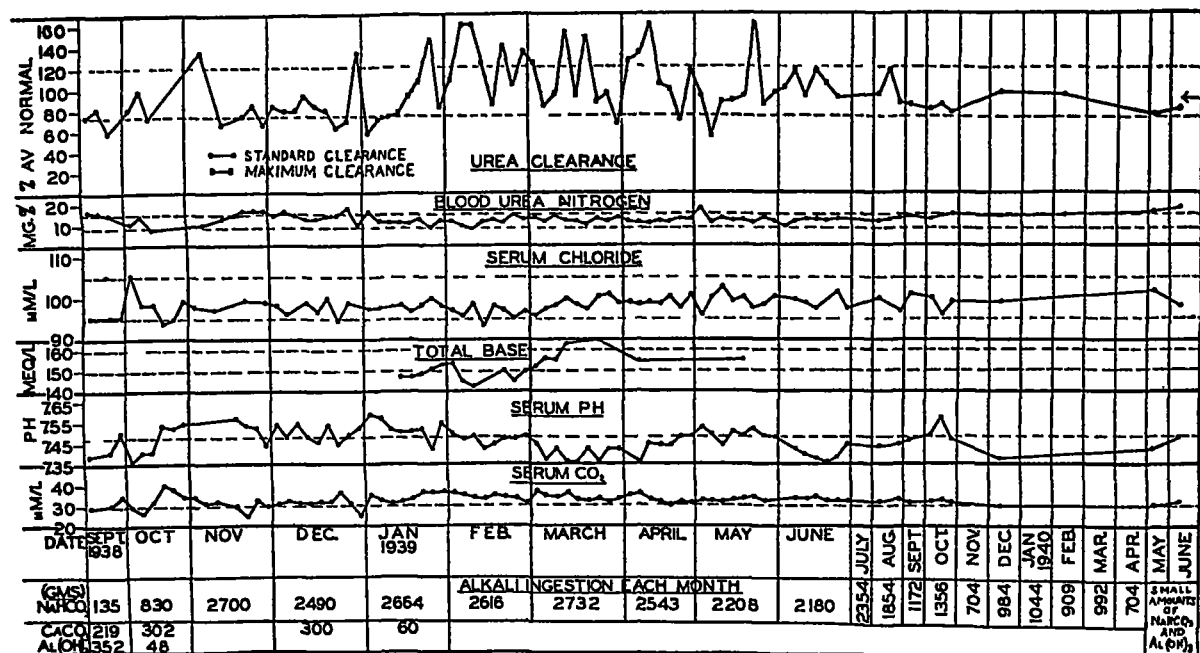


FIG 1 Serum electrolytes and urea clearance during continued sodium bicarbonate administration

day. The total amount of alkali administered during the 20 months between September 6, 1938, and April 22, 1940, consisted of 400 c c of aluminum hydroxide, 881 grams of calcium carbonate and 31,414 grams of sodium bicarbonate. Alkalis were taken only occasionally during the final seven months (April 23, 1940, to November 13, 1940), and the intake was comparatively small.

Routine Laboratory Data and Clinical Course The red and white blood cell counts and the hemoglobin remained within normal limits. Three histamine tests (0.6, 0.6, 0.65 mg.) disclosed a maximum free acidity of 118, 110, and 150 clinical units respectively. Forty-five urine specimens were examined, the specific gravity varied from 1.015 to 1.034, averaging 1.024, the reaction was constantly alkaline; a trace of albumin was detected on four occasions. Numerous electrocardiograms revealed no significant changes. The patient's clinical course was entirely uneventful. His body weight gradually increased from 54 kg to 66 kg during the 27 month period of observation. The ulcer crater disappeared in five weeks and did not reappear.

Acid Base Balance The acid base balance was determined 78 times during the present study (see chart). The serum CO₂ during the period of hospitalization varied usually from 31 to 35 mM/L (normal 20–30 mM/L) with increases to 37.7 and 39.2 mM/L on two occasions. After discharge from the hospital (August 1, 1939, to November 13, 1940) the CO₂ remained within normal limits. The serum pH paralleled the CO₂ and fluctuated usually from 7.33 to 7.50 (normal 7.35 to 7.45), although values between 7.50 and 7.53 were noted frequently. The total base was determined on 18 occasions, only two of the results (163.4 and 164.9) exceeded

the normal range of 150 to 160 milliequivalents per liter. The serum chloride was consistently within the normal limits of 95 to 105 millimols per liter.

Renal Function Two urine concentration tests before alkali therapy revealed maximum specific gravities of 1.025 and 1.027. Three urea clearance tests during the control period measured 60, 75 and 80 per cent of average normal respectively (lower limit of normal considered to be 75 per cent). The urea clearance subsequently was determined on 75 occasions in the succeeding 27 months, 30 of these were by the standard clearance with urine volumes never less than 1 c.c. per minute. Forty-five of the determinations were by the maximum clearance, the urine volumes varied from 21 to 92 c.c. per minute. The urea clearance was below 75 per cent on 10 occasions, the other 65 clearances fluctuated within the normal range of 75 to 150 per cent. It is of interest to note that the two final clearances of 75 and 80 per cent, after the administration of 33,000 grams of alkali, duplicated exactly the values obtained before alkali therapy.

Blood Urea Nitrogen The blood urea nitrogen remained normal throughout the entire study. The results ranged from 8.2 to 16.5 mg. per cent with an average of 11 to 12 mg. per cent.

COMMENT

The administration of large quantities of sodium bicarbonate results usually in an elevation of the serum CO_2 and a corresponding secondary reduction of the serum chloride. The urinary excretion of the titratable acid plus ammonia falls while the bicarbonate content and pH of the urine rise. Palmer and Van Slyke⁷ found that following the administration of sodium bicarbonate the plasma bicarbonate of patients with nephritis often rose considerably higher than the level seen in normal individuals before the urine became alkaline. Ellis⁸ observed a definite bicarbonate excess and a high serum pH in a nephritic patient with acid urine, and others^{9,10} have reported similar findings. Alkalosis following the ingestion of sodium bicarbonate apparently represents merely a retarded excretion of bicarbonate. The remarkable tolerance to sodium bicarbonate exhibited by our patient may be attributed, therefore, to the excellent function and reserve capacity of the kidney, as well as to the large volume of fluid available for excretion of the alkali.

The absence of demonstrable renal injury after the administration of massive quantities of sodium bicarbonate in this patient is in accord with recent clinical observations indicating that alkalis per se do not cause intrinsic renal disease. The fact that alkali therapy may be continued for years without permanent depression of the urea clearance has been mentioned previously. Evidence likewise has been obtained suggesting that hypochloremia and dehydration may be of great etiologic importance in the development of alkalosis.¹¹ The impairment of renal function observed during alkalosis usually disappears promptly after correction of the acid base disturbance. The rapidity with which renal efficiency may be restored indicates that no intrinsic injury to the kidney occurred, an observation which gains further support by the failure of Hoag et al.¹² to observe anatomic changes in the kidney of the experimental animal after the subcutaneous and intravenous injection of therapeutic doses of sodium bicarbonate. Kirsner¹³ administered massive quantities of sodium bicarbonate both orally and intravenously to a series of dogs for as long as nine months without producing any significant morphologic changes in the kidney, even though alkalosis had been induced repeatedly. It is obvious from these studies that the

normal kidney can cope successfully with excesses of alkali for a prolonged time without untoward effects provided adequate amounts of fluid and of salt are available

SUMMARY

The administration of 32,000 grams of sodium bicarbonate in 20 months to a patient with normal renal function produced no marked alteration in the acid-base balance and no decrease in the urea clearance

BIBLIOGRAPHY

- 1 KIRSNER, J B, and PALMER, WALTER LINCOLN Alkalosis complicating the Sippy treatment of peptic ulcer An analysis of 135 episodes, *Arch Int Med*, 1942, *lxix*, 789
- 2 BERGER, E H Importance of kidney function in alkalosis, *Northwest Med*, 1937, *xxxvi*, 125
- 3 JEGHERS, H, and LERNER, H H The syndrome of alkalosis complicating the treatment of peptic ulcer Report of cases with a review of the pathogenesis, clinical aspects, and treatment, *New England Jr Med*, 1936, *ccxiv*, 1236
- 4 PETERS, J P, and VAN SLYKE, D D Quantitative clinical chemistry, Vol 2, Methods, 1931, Williams and Wilkins, Baltimore, pp 835, 283, 796, 367
- 5 VAN SLYKE, D D, AND OTHERS Observations on the course of different types of Bright's disease and resultant changes in renal anatomy, *Medicine*, 1930, *ix*, 257
- 6 STADIE, W C, and ROSS, E C Micro method for determination of base in blood and serum and other biological materials, *Jr Biol Chem*, 1925, *xlvi*, 735
- 7 PALMER, W W, and VAN SLYKE, D D Studies of acidosis IX Relationship between alkali retention and alkali reserve in normal and pathological individuals, *Jr Biol Chem*, 1917, *xxxii*, 499
- 8 ELLIS, A W M Disturbance of the acid base equilibrium to the alkaline side, alkalemia, *Quart Jr Med*, 1924, *xvii*, 405
- 9 HARROP, G A, JR Production of tetany by intravenous infusion of sodium bicarbonate report of adult case, *Bull Johns Hopkins Hosp*, 1919, *xxx*, 62
- GRANT, S B Tetany—a report of cases with acid base disturbance, *Arch Int Med*, 1922, *xxx*, 355
- MORSE, J L An unusual case of alkalosis and impairment of the excretory power of the kidneys, *New York Med Jr*, 1920, *cxii*, 965
- 10 PETERS, J P, and VAN SLYKE, D D Quantitative clinical chemistry, Vol I, Interpretations, 1931, Williams and Wilkins, Baltimore, p 974
- 11 KIRSNER, J B, and PALMER, WALTER LINCOLN The rôle of chlorides in alkalosis following the administration of calcium carbonate, *Jr Am Med Assoc*, 1941, *cxvi*, 384
- 12 HOAG, L A, WEIGELE, C E, TALAMO, H, MARPLES, E, and WOODWARD, K Effect of therapeutic doses of sodium bicarbonate on the kidneys, *Jr Pharmacol and Exper Therap*, 1933, *xlvi*, 233
- 13 KIRSNER, J B . The effect of the prolonged administration of large quantities of sodium bicarbonate on the kidney of the dog, *Arch Path*, 1941, *xxxii*, 76

EXFOLIATIVE DERMATITIS DUE TO PHENOBARBITAL: REPORT OF A CASE WITH RECOVERY *

By SHERWOOD W BAREFOOT, M D, and J LAMAR CALLAWAY, M D,
Durham, North Carolina

SINCE their introduction for clinical use in 1913, the barbiturates have found an increasingly prominent and deserved place among the commonly used sedatives. The increasing number of reports during recent years regarding their toxic reactions is an indication of their popularity.

The incidence of toxic reactions due to the barbituric acid derivatives varies considerably in different hands. Fifteen years after their introduction Menninger,¹ after a thorough review of the literature, was able to find only 41 instances of cutaneous eruptions attributed to barbiturates. To this list, he added three of his own cases. In 1927 Jackson² reported six instances of skin rash in a series of 500 patients treated with phenobarbital. Contrasted with these low figures, Scarlett and MacNab,³ in 1935, stated that they encountered such frequent toxic reactions from phenobarbital that they were no longer using the drug except in instances of severe convulsive seizures.

In the Duke Hospital Clinic cutaneous manifestations of toxicity from barbiturates have been rare, and this report deals with the only recognized instance of any clinical consequence. In the Duke Clinic, when prolonged administration of a sedative is desired, barbiturates are generally given preference over bromides since the toxic reactions from the former have been much less in evidence than the disturbing mental symptoms produced by the prolonged ingestion of bromides.⁴

It is now common knowledge that the administration of barbiturates may be followed by a dermatitis medicamentosa which usually subsides promptly when the drug is withdrawn. The occurrence of exfoliative dermatitis following the ingestion of barbiturates, however, is so rare that these drugs have not in the past been considered as an important etiological factor. The incidence of such occurrences, when compared with the number of persons receiving these drugs is, certainly, extremely small. When such a reaction occurs it is of grave significance, since it is accompanied by severe systemic manifestations, and the majority of such patients do not recover. It is, therefore, important that physicians be acquainted with the fact that barbituric acid derivatives may produce such serious consequences.

In all cases of exfoliative dermatitis of obscure origin in which the onset was preceded by the ingestion of barbiturates or drugs of obscure origin, it would seem advisable to use a sedative not derived from barbituric acid, since in such instances one may be dealing with a case in which one of the barbiturates is the etiological agent.

In 1919 Hueber⁵ described a fatal case of "chronic infiltrating desquamating eczema covering the whole body, palms and soles" following the administration of phenobarbital. This may have represented a case of exfoliative dermatitis, but credit for first reporting a case of exfoliative dermatitis due to phenobarbital

* Received for publication May 3, 1941.

From the Section of Dermatology and Syphilology of the Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

is given to Hamilton, Geiger, and Roth.⁶ In 1926 they described a case in which there was loss of the integument including the finger and toe nails as well as part of the hair. Their patient recovered after a prolonged illness. In 1927 Jackson² reported a case of generalized desquamation, but the desquamation was preceded by vesiculation. We are not accepting this patient as an instance of exfoliative dermatitis, since only those cases in which the appearance was that of an arsenical exfoliative dermatitis, as was the case in our patient, are included. In 1929 Chavany and Vannier⁷ reported two cases with fatal outcome, and Poole⁸ described a case with death. In 1932 Lancaster⁹ reported an instance similar to ours in that exfoliative dermatitis followed the ingestion of phenobarbital on two different occasions, and was followed by complete recovery in each instance. Millard¹⁰ in 1933 reported an instance of universal exfoliative dermatitis with a fatal termination following the administration of phenobarbital. In 1934 Haubrick¹¹ described a case of exfoliative dermatitis following the ingestion of phenobarbital with recovery. In 1935 Hickmann¹² described a case of generalized exfoliation including the hair with a fatal outcome, and in Canada Scarlett and MacNab³ reported the sixth fatal case attributed to phenobarbital. There was generalized desquamation but here, again, the exfoliation was preceded by a bullous eruption and we are not including this as a case of exfoliative dermatitis. A fatal case of exfoliative dermatitis following the administration of phenobarbital was presented by Sweitzer and Layman¹³ in 1937. Wile and Benson¹⁴ in 1940 reported two fatal cases. The most recent reports were made by Sexton, Pike, and Nielson¹⁵ in February 1941 in which they described one fatal case, and by Winer and Baer¹⁶ in 1941 who reported a fatal case of exfoliative dermatitis due to phenobarbital with clinical and postmortem studies.

In the literature we have found 13 cases which appear to have been examples of true exfoliative dermatitis following the ingestion of barbiturates, and in 10 of these the outcome was fatal. We are reporting a single instance with recovery. In this patient the etiological diagnosis seems definitely established since, on two occasions, the ingestion of phenobarbital was followed by an exfoliative dermatitis.

CASE REPORT

Mrs I B, a 58-year-old white housewife, was admitted to Duke Hospital on April 4, 1940. Her complaint was desquamating dermatitis with onset 10 days previously. There were no pertinent findings in her family history, and there was no history of allergy. Marital history was non-contributory.

The patient's general health had been good until 10 years previously, at which time she developed a right hemiplegia following a severe epistaxis. The paralysis cleared up without residual symptoms within a few months. She had experienced an uneventful menopause five years previously. No allergy nor known idiosyncrasies were present. Five months prior to admission she had been ill with "flu" and had not felt as well as usual since that time, having complained of weakness and nervousness. A review of the dietary history revealed a low protein intake.

Ten days prior to admission, the patient noticed that her face seemed to be sunburned, and on the following day there was erythema of the entire body. She consulted her physician who advised her to discontinue the 0.032 gr tablets of phenobarbital three times daily which he had prescribed five days previously and gave her

soothing lotions to apply locally. Severe generalized pruritus developed, and within two or three days after the onset there was considerable exfoliation and the corners of the mouth and palms became fissured.

Physical examination revealed temperature to be 38.4°C , pulse 95, respirations 20, blood pressure 160 mm Hg systolic and 84 mm diastolic. The patient was a moderately obese white female in obvious discomfort and complaining of chilliness. There was generalized erythema with thickening of the skin over the face and extremities. The skin of the palms was greatly thickened, and the palms and corners of the mouth were fissured. The scalp showed considerable scaling. There was no lymphadenopathy. The tongue showed atrophic papillae. There were several carious teeth and considerable periodontal infection. The tonsils showed evidence of chronic infection. The lungs were clear. The heart was not enlarged and auscultation was negative except for a soft apical systolic murmur. The peripheral vessels showed moderately advanced arteriosclerosis. Abdominal, pelvic, and rectal examinations were negative. There was slight pitting edema of both ankles (note low serum proteins). Neurological examination was negative except for slight impairment of vibratory perception below the knees.

Accessory Clinical Findings Hemoglobin 12.4 grams (Sahli) or 80 per cent. Red blood cells 3,650,000 cells per cubic millimeter. White blood cells 9,600 cells per cubic millimeter. Differential count: Polymorphonuclears 65 per cent, lymphocytes 13 per cent, monocytes 3 per cent, eosinophiles 17 per cent, basophiles 2 per cent. Smear of the peripheral blood was not remarkable. Sedimentation rate 5 millimeters per hour, corrected (normal). Urine negative on repeated examinations, and a catheterized specimen was sterile on culture. A 24 hour urine specimen was negative for arsenic. Stool was negative for parasites and blood, and on culture showed no unusual organisms except for a few colonies of hemolytic *E. coli*. Blood culture was sterile. Throat culture showed colonies of non-hemolytic *Staphylococcus aureus* and alpha streptococci. Culture of bile removed by duodenal intubation was sterile. Studies of the fasting gastric contents showed the presence of a normal amount of free hydrochloric acid. Chemical analysis of the blood showed the following findings: non-protein nitrogen 29 mg per cent, fasting sugar 82 mg per cent, plasma chlorides 608 mg per cent, total serum proteins 4.6 grams per cent, albumin 2.8 grams per cent, globulin 1.8 grams per cent. The albumin-globulin ratio was lowered, being 1.5. Roentgenogram of the chest showed widening and tortuosity of the aorta, but the heart was of normal size and shape. The lungs appeared to be normal. Plain roentgenogram of the abdomen showed no visceral abnormalities. The lumbar spine exhibited considerable hypertrophic arthritic changes. Oral cholecystogram showed normal filling and emptying of the gall-bladder. Roentgenograms of the sinuses were negative. Electrocardiogram showed no changes indicative of myocardial disease.

Course in the Hospital During the first week in the hospital, the patient had a low grade fever which was seldom above 38°C . After the first week, the temperature was normal. By the end of the first hospital week the skin over the entire body was exfoliating. After another week the exfoliation practically subsided and the skin gradually assumed a normal appearance.

Approximately one week after admission the patient developed a mild bilateral conjunctivitis, which was treated with the instillation of a 2 per cent solution of boric acid and subsided within a period of 10 days.

Local treatment to the skin consisted of starch baths and soothing lotions containing large amounts of olive oil. Ten c.c. of a 10 per cent solution of calcium gluconate intravenously, and 10 c.c. of autogenous blood intramuscularly were administered on alternate days. She was also given concentrates of all the known vitamins as well as iron.

During the last week in the hospital the lower bicuspid and tricuspid were extracted, and a tonsillectomy and adenoidectomy were performed with no untoward results. The blood cytology remained essentially the same throughout the hospital stay with the eosinophilia gradually becoming less marked. The ankle edema, present on admission, subsided after the patient had been placed upon a dietary régime which included an adequate protein intake.

She was discharged May 9, 1940 with a diagnosis of exfoliative dermatitis of unknown origin. The cutaneous manifestations had completely subsided at the time of discharge.

Course after Discharge from Hospital On June 4, 1940, about one month after discharge, the patient appeared in the Out Patient Clinic complaining of generalized pruritus. There was generalized erythema of the skin and the eyelids were edematous. She stated that the onset had occurred two days previously after she had taken 0.032 gram of phenobarbital on the preceding night. This was the first time that she had taken any barbiturate since leaving the hospital. With this information, we for the first time felt justified in attributing the previous episode to the ingestion of phenobarbital.

The patient has not been seen again since she lives at a distance of several hundred miles from Duke Hospital. We have, however, corresponded with her and in a communication dated June 28, 1940 she stated that following her visit to the Clinic the skin over the entire body had desquamated. She said that the sequence of the cutaneous manifestations had been identical with those of the previous episode, and that she had completely recovered.

COMMENT

Judging from the reports in the literature, and from our personal experience, the occurrence of exfoliative dermatitis following the administration of barbituric acid derivatives is quite rare. In our opinion, the causative agent in the case which we are reporting seems to be definitely established. The ingestion of phenobarbital on two different occasions was followed by an exfoliative dermatitis. Clinically, the cutaneous lesions could not be distinguished from an exfoliative dermatitis produced by arsenic. It is interesting to note that our case, as well as a good many of the reported cases, developed a conjunctivitis. This may be of some diagnostic value in as much as we have never seen this manifestation in a case of exfoliative dermatitis due to arsenic.

In the majority of the reported cases developing an exfoliative dermatitis following the ingestion of barbiturates, the outcome has been fatal. The gravity of the complication does not seem to be dependent upon the amount of the drug ingested. In our patient, the second episode followed the ingestion of only 0.032 gram of phenobarbital, whereas in other hands manifestations of serious complications did not appear until large amounts of the drug had been administered.

In the reports of the fatal cases of exfoliative dermatitis following the administration of barbiturates, no adequate explanation for the cause of death has been offered. Hueber's⁵ case became uremic, but this seems to be an exception. Autopsies, when performed, have shown little other than terminal bronchopneumonia. Winer and Baer¹⁶ found eosinophilia and severe vascular involvement of several internal organs, as well as tuberculoid structures in the spleen, in their case and felt that these tissue reactions were based on an allergic reaction.

SUMMARY

1 In our experience, phenobarbital has proved to be a valuable sedative and toxic reactions have been very rare

2. Barbituric acid derivatives, however, may be responsible for serious consequences including an exfoliative type of dermatitis which cannot, clinically, be distinguished from an exfoliative dermatitis produced by arsenic

3 Patients with exfoliative dermatitis produced by barbiturates seem to have a tendency to develop conjunctivitis, which is quite rare in exfoliative dermatitis produced by other substances

4 The prognosis in cases of exfoliative dermatitis due to barbiturates is grave and the systemic reactions are, as a rule, quite severe In 12 previously reported cases, nine had a fatal outcome

5 Clinical and postmortem studies have offered no satisfactory explanation in the majority of the fatal cases as to the cause of death

6 The amount of barbituric acid derivatives ingested seems to have no relationship to the severity of the toxic reaction

7 In treating patients with exfoliative dermatitis of obscure origin who give a history of ingestion of barbiturates or other preparations of unknown composition, it would seem advisable to use drugs other than barbituric acid derivatives for sedation

8 A case of exfoliative dermatitis which has been thoroughly studied and in which the administration of phenobarbital on two different occasions was followed by exfoliative dermatitis is reported

BIBLIOGRAPHY

- 1 MENNINGER, W C Skin eruptions with phenobarbital (luminal), Jr Am Med Assoc., 1928, xci, 181
- 2 JACKSON, A S Toxic reactions from phenobarbital (luminal), Jr Am Med Assoc., 1927, lxxviii, 642-643
- 3 SCARLETT, E P, and MACNAB, D S Poisoning from phenobarbital (luminal), Canad Med Assoc. Jr, 1935, xxxiii, 635-641
- 4 HANES, F M, and YATES, A Analysis of four hundred instances of chronic bromide intoxication, South Med Jr, 1938, xxxi, 667-671
- 5 HUEBER, E Ein Fall von Luminalvergiftung mit todlichem Ausgang, Munchen med Wchnschr., 1919, lxi, 1090
- 6 HAMILTON, E S, GEIGER, C W, and ROTH, J H Luminal poisoning with conjunctival residue, Illinois Med Jr, 1926, xlix, 344-346
- 7 CHAVANY, J A, and VANNIER, P E Toxidermie barbituaigue a type d'erythème scarlatiniforme infiltré, Progrès med., 1929, xlv, 1685-1693
- 8 POOLE, A K Drug reactions from barbital and phenobarbital, Yale Jr Biol and Med, 1929, i, 345-351
- 9 LANCASTER, A H Luminal dermatitis with case reports, South Med Jr, 1932, xxv, 1142-1145
- 10 MILLARD, R J Three cases of 'luminal' poisoning, Med Jr Australia, 1933, ii, 518-519
- 11 HAUBRICK, B P Phenobarbital poisoning, New England Jr Med, 1934, ccxi, 264-267
- 12 HICKMANN, M Luminalkrankheit unter dem Bilde der Dermatitis exfoliativa mit todlichem Ausgang, Ztschr f Kinderh., 1935, lvi, 358-360
- 13 SWEITZER, S E, and LAYMAN, C W Severe cutaneous reactions to the barbiturates, Minnesota Med, 1937, xx, 92-96

- 14 WILE, U J, and BENSON, J A Exfoliative dermatitis due to phenobarbital with fatal outcome, report of two cases, ANN INT MED, 1940, xiii, 1243-1249.
- 15 SEXTON, D L, PIKE, G M, and NIELSON, A Exfoliative dermatitis and death due to phenobarbital, Jr Am Med Assoc, 1941, cxvi, 700-701
- 16 WINER, N J, and BAER, R L Exfoliative dermatitis due to phenobarbital, Arch Dermat and Syph, 1941, xliii, 473-484

POSTOPERATIVE PRECIPITATION OF VITAMIN DEFICIENCIES *

By MAX ELLENBERG, M D, HENRY DOLGER, M D, and HERBERT POLLACK, M D, F A C P, *New York, N Y*

PROLONGED chronic illnesses are often accompanied by anorexia and not infrequently by vomiting. In many instances, the nature of the illness may necessitate a restricted diet such as a low residue or bland diet for prolonged periods. By the time the patient enters the hospital he may, therefore, be in a state of partial vitamin depletion.

The preoperative preparation of the patient usually includes a sharply limited diet, especially when surgery of the gastrointestinal tract is contemplated. Preparation not infrequently includes the administration of intravenous fluids, adding the effect of an induced diuresis which would tend to deplete the body stores of the water soluble vitamins. Most parenteral fluids routinely contain glucose. The drain of a high carbohydrate metabolism on the vitamin B stores in the body has been recognized.

The insult of the operative trauma itself, as well as the deleterious effect of a prolonged anesthesia on the liver and other organs, would tend to disrupt the mechanism of the vitamin actions.

During the postoperative period, postanesthetic nausea and vomiting occur frequently. There is the necessity for complete restriction of food for a time, often after partial or total gastrectomy no food is given for days. The fluid balance is maintained by the long continued use of intravenous fluids which again usually contain glucose.

All the above enumerated factors add up on the debit side of nutritional balance and form a readily understandable background for the development of the observed vitamin deficiencies. The case herein presented fits into this picture very clearly.

CASE REPORT

K U, a 75-year-old white male, was first admitted to the Mount Sinai Hospital in November 1938. For one year he had been suffering from epigastric pain unrelated to meals, constipation, loss of weight, and anorexia. A barium enema disclosed a stenosing lesion in the proximal portion of the transverse colon, having the appearance of a neoplasm. The patient refused operation and returned home. He was readmitted to the hospital in May 1940. In the intervening year and a half, he had had recurrent episodes of abdominal pain, progressively becoming more severe.

* Received for publication June 18, 1941.

From the Metabolism Clinics and the Surgical Services of The Mount Sinai Hospital, New York City.

Anorexia continued throughout this period and he lost an additional 20 pounds in weight. During the week immediately preceding this admission, he had had severe cramp-like abdominal pain and frequent, repeated vomiting. He presented the classical picture of subacute intestinal obstruction. A barium enema again revealed an obstructing lesion in the proximal portion of the transverse colon. He was treated preoperatively with a continuous intravenous infusion of 5 per cent glucose in saline and an indwelling Levine tube. Four days later, under general anesthesia, a partial colectomy with removal of a malignant tumor was performed and a temporary colostomy was established. The continuous intravenous infusion was maintained for five days postoperatively. Not until one week after operation was the patient started on a low residue diet.

The nurses' records at this time, one week after operation, made note of the patient's complaint of a sore, burning mouth. In spite of frequently repeated, painstaking oral hygiene, he still complained of the pain in the mouth. This rapidly became worse to the point that any attempt at eating or drinking resulted in such marked exacerbation of the discomfort that the patient literally went on a hunger strike. His mental state changed so that he was uncooperative, disoriented and confused. The dental department saw him at this time and noted "poor oral hygiene, distributed over the mucosa of the lips, cheeks, vestibule, hard palate, fauces and gingiva are flat, light tan-colored serpiginous patches with a red border." He was treated locally with gentian violet, but the lesions still progressed. Two days later, when seen by us, there were in addition, ulcers and bullae on the oral mucous membrane. The tongue was moderately smooth, but not fiery red. The gums were heaped up, edematous and reddish-purple in color. He complained bitterly of burning of the mouth and refused water almost as one with hydrophobia.

Because of the relatively slight involvement of the tongue, he was started on riboflavin concentrate, equivalent to 10 mg, three times a day. After 24 hours there was still extension of the lesion. Therefore, he was further treated with 300 mg of nicotinic acid intravenously, administered in three divided doses each day. There immediately ensued a most dramatic change. Overnight there was a marked decrease in his symptoms and he began to eat. His mental state cleared rapidly. Objectively, within 24 hours, the angry, gray slough overlying the ulcers cleared considerably. Within five days the lesions had entirely disappeared. His appetite improved considerably. Within two weeks, he had recuperated sufficiently to permit the surgeons to proceed with closure of the colostomy. During the second operative period vitamin therapy was maintained. There was no recurrence of the lesion.

The history, the preliminary chain of events, the nature of the lesions, the mental symptoms, and the clear-cut rapid complete response to the administration of specific vitamin therapy support the diagnosis of a vitamin B complex deficiency, predominantly of niacin.

EDITORIAL

HYPERGLYCEMIA AND GLYCOSURIA AS MEANS OF CONTROLLING PROTAMINE ZINC INSULIN ADMINISTRATION IN DIABETES

BEFORE insulin was discovered dietary restriction and control constituted the only therapeutic procedures which materially affected the course of diabetes. As a guide to the effectiveness of treatment, hyperglycemia and the attendant glycosuria were universally employed. Control of the glycosuria was followed by improvement, whereas failure to accomplish this meant active and progressive disease. Naunyn (1906) was among the first to formulate this observation precisely: "In many cases of diabetes glycosuria shows a decided tendency to progress. But in the majority of cases the progressiveness of the glycosuria is only the expression of the bad influence which the glycosuria itself exerts on the tolerance. The glycosuria should be abolished on account of the favorable influence which the aglycosuric condition has on tolerance." It is not sufficient "to maintain the patient for a long time in an endurable condition of life. Treatment includes a broader, more definite purpose, namely to strengthen (to improve) a disturbed function or at least to stop its further deterioration (the progressive development of the disease)." ¹ Many confirmatory observations have been made in experimentally produced diabetes in animals. It was but natural to conclude that, since hyperglycemia and glycosuria are signs of ill omen, they are presumably in themselves directly injurious.

The introduction of soluble insulin increased enormously the effectiveness of treatment. For the more severe types of the disease, however, it can not be said to have simplified treatment as much as might be desired. Abolition of glycosuria and control of hyperglycemia have been the criteria of successful management, and in order to accomplish this it is often necessary to distribute the food with painstaking care and administer three or four doses of insulin a day.

The introduction of the relatively insoluble and slowly absorbed protamine zinc insulin promised to simplify procedures greatly. As the effect of a single dose, if not too small, is maintained in some degree for 24 hours or more, it became possible, theoretically at least, to administer the entire daily requirement in a single early morning dose. Although this has proved highly satisfactory in the mild cases, in the more severe cases it is often difficult or impossible to abolish glycosuria without incurring severe insulin reactions. This has been combated by redistribution of the diet, but often an extra morning dose of soluble insulin, or even two or three such doses are required if the usual criteria for adequate control are to be fully met. Such

¹ As translated by JOSLIN, E. P. The campaign against diabetes (correspondence), Jr. Am. Med. Assoc., 1942, cxxx, 860.

difficulties have led some clinicians to feel that adequate control of severe cases with protamine insulin alone is impracticable if not impossible

As insulin reactions are much more disturbing and probably more dangerous than a moderate glycosuria, inevitably some patients were maintained on a régime which resulted in the excretion of substantial amounts of glucose. This was found not to be followed by any immediate obvious injury. Even as meticulous and conservative a clinician as Joslin² regarded control as adequate if the patient was otherwise in satisfactory condition and if the glucose excreted did not exceed 10 per cent of the carbohydrate intake. Others have been much more daring. Thus Tolstoi and Weber³ reported careful metabolic studies on two patients with severe diabetes who were maintained on an adequate diet and given one daily dose of protamine zinc insulin which just failed to cause hypoglycemic reactions. These patients felt well, were in nitrogen equilibrium and showed only trivial fluctuations in weight in spite of constant heavy glycosuria. These observers⁴ later reported a study of 84 cases followed for one year in the out patient department and treated in a similar manner with no special effort to keep the urine free from sugar. Of these, 27 patients excreted glucose persistently and in large amounts. Nevertheless they continued at work, with four exceptions maintained or increased their weight, were free from symptoms and were believed to be as free from infections as the group whose urine was substantially sugar free. The authors concluded that glucose must have been utilized in quantities adequate for their needs, and that the important factor in treatment "is not how much sugar is excreted, but how much is utilized." They therefore suggested as criteria of satisfactory treatment, maintenance of weight, absence of ketosis, freedom from the usual symptoms of diabetes and avoidance of hypoglycemic reactions. Under such circumstances they believe glycosuria and hyperglycemia are immaterial and may be even advantageous in as far as the latter protects from hypoglycemic insulin reactions.

Partly in answer to criticisms of this procedure by Joslin⁵ and others, in a recent number of the ANNALS OF INTERNAL MEDICINE Tolstoi, Almy and Toscani⁶ again have reported a metabolic study of a man with severe diabetes treated successfully by this method, according to their standards. Although the patient constantly excreted large amounts of glucose over the six weeks' period, he was in positive nitrogen balance, maintained weight

² JOSLIN, E. P. Diabetes and protamine insulin, *Mil Surg*, 1938, lxxxii, 1.

³ TOLSTOI, E., and WEBER, F. C., JR. Protamine zinc insulin: a metabolic study. Treatment in two severe cases of diabetes with equally and unequally divided diets, with comments on criteria for treatment, *Arch Int Med*, 1939, lxiv, 91-104.

⁴ TOLSTOI, E., and WEBER, F. C., JR. Protamine zinc insulin: a clinical study. Report of a group of diabetic patients in whose cases glycosuria was disregarded for one year, *Arch Int Med*, 1940, lvi, 675-678.

⁵ JOSLIN, E. P. Treatment of diabetes (correspondence), *Jr Am Med Assoc*, 1940, cxv, 1038-1039.

⁶ TOLSTOI, E., ALMY, T. P., and TOSCANI, V. Treatment of diabetes mellitus with protamine insulin: is a persistent glycosuria harmful? A metabolic study of a severe case, *ANN INT MED*, 1942, xvi, 893-903.

and was free from symptoms. Previous attempts to control the glycosuria by multiple doses of soluble insulin had not given as satisfactory clinical results. In spite of marked glycosuria over a period of three years, this patient is reported to have shown no special susceptibility to infection, no impairment of renal function and no demonstrable increase in atherosclerosis. They reaffirm their belief that glycosuria is harmless if adequate utilization of carbohydrate is secured (by the use of protamine zinc insulin).

These views have been severely criticized, largely on the ground that hyperglycemia is directly harmful in itself. It has been regarded as a direct stimulus to insulin secretion, and overstimulation of a diseased organ may be expected to damage it still further. Hyperglycemia is also generally blamed for the susceptibility to infection and the tendency to atherosclerotic changes so characteristic of uncontrolled diabetes, although there is no real proof that they are simply a direct result of hyperglycemia.

The formerly held concept that the primary fault in diabetes is loss of the ability to utilize carbohydrate and that insulin acts simply by bringing about better utilization is not an adequate explanation of the metabolic disturbances in this disease. Perhaps equally important are the inability to store carbohydrate as glycogen, and the tendency to excessive gluconeogenesis from protein. These disturbances are also controlled by insulin. Furthermore the completely diabetic animal retains the capacity to utilize significant amounts of carbohydrate, provided there is an extreme degree of hyperglycemia or great undernutrition. Neither is the height of the blood sugar a reliable indication of the degree to which glucose is utilized. Thus Bridge and Winter⁷ have shown that in patients under treatment, fluctuations in the blood sugar from 100 to 300 mg per cent in the course of the day are not accompanied by corresponding or significant changes in the respiratory quotient. It seems clear that hyperglycemia can not be accepted as the sole criterion of adequate control and is probably not the most important single criterion.

Although it is difficult to determine directly the harm caused by hyperglycemia itself in human diabetes, there is highly suggestive evidence in animal experiments that hyperglycemia is harmful in itself. In the dog and in the partially depancreatized cat, as shown for example by Lukens and Dohan,⁸ repeated injections of anterior pituitary extract can produce a permanent and progressive diabetes associated with histological changes in the islands of Langerhans. If, however, insulin was administered, or if the cats were fasting or if they were on a high fat, low protein diet, permanent diabetes would not develop. Furthermore, if treatment of the established diabetes was started early before irreversible changes in the islands had occurred, either by the administration of insulin or by a reduction of the meat in the diet, the disease could be arrested and the islands recover normal struc-

⁷ BRIDGE, E. M., and WINTER, E. A. Diabetes, insulin action and the respiratory quotient, *Bull. Johns Hopkins Hosp.*, 1939, **LXIV**, 257.

⁸ LUKENS, F. D. W., and DOHAN, F. C. Pituitary diabetes in the cat, recovery following insulin or dietary treatment, *Endocrinology*, 1942, **xxx**, 175-202.

ture, and a full diet could be resumed later without recurrence of the diabetes. In general, diabetes with injury to the islands developed only under conditions which caused a persistent hyperglycemia, and it was arrested by procedures which abolished hyperglycemia. It was even possible to cure the diabetes by lowering the blood sugar with phlorhizin, which as far as is known lowers blood sugar solely by increasing glycosuria. Although alternative explanations of the effect of diet on this experimental diabetes can be offered, the weight of evidence against hyperglycemia seems strong. These observations indicating the direct harmfulness of hyperglycemia in animals, however, can not be applied to man without further study.

As far as the general management of human diabetes is concerned, in the light of present knowledge it would not seem prudent to disregard hyperglycemia and glycosuria. This would encourage carelessness in treatment and possibly lead to the injury of many patients. In patients who are receiving protamine zinc insulin, a moderate degree of glycosuria appears to be harmless. For the present, however, a real effort should be made to avoid persistent and marked glycosuria. How marked a degree of glycosuria can safely be disregarded and how far the effort to control it should be carried are the questions at issue, and at present no final answer to them can be given. It would seem that the effort should at least include careful control and, if necessary, redistribution of the diet and one supplementary morning dose of soluble insulin. In the relatively small group of patients of whom control is difficult, it may well be better to disregard glycosuria, if conditions are otherwise satisfactory, rather than risk hypoglycemic reactions or insist upon a complicated and burdensome régime which interferes with their normal activities. Tolstoi has shown that patients can be so maintained in a state of comfort and efficiency and with no injury obvious, at least during a three or four years' observation period. Until it has been demonstrated that hyperglycemia can be endured without injury over a much longer period, however, it would be unwise to encourage disregarding it in the routine treatment of diabetes.

REVIEWS

Introduction to Physical Biochemistry By J M JOHLIN, Ph D, D Sc 231 pages, 24 × 16.5 cm Paul B Hoeber, Inc, New York 1941 Price, \$2.75

According to the author much of the material in the book under review has been presented to his students of biochemistry, as a preliminary survey of some of the fundamental facts which they must know for a better understanding of various biological phenomena and of laboratory procedures. The introduction includes a short chapter on the functions and composition of blood. Then follow concise but adequate chapters on the physical and chemical properties of water, hemoglobin, the gas laws, the colligative properties of solutions, the characteristics of the colloidal state of matter, chemical equilibrium and the law of mass action, buffer systems, the properties of indicators, oxidation-reduction potentials, the respiratory functions of blood, the acid-base balance of the blood, and, finally, a chapter on oxidation-reduction systems. In addition a chapter on logarithms has been added. This book should prove valuable to the student or clinician who desires an increased knowledge of these subjects.

E G S

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Cancer of the Uterus By ELIZABETH HURDON, C B E, M D 188 pages, 22 × 14.5 cm 1942 Oxford University Press, New York Price, \$5.00

Practical Survey of Chemistry and Metabolism of the Skin By MORRIS MARKOWITZ, M D 196 pages, 20.5 × 13.5 cm 1942 The Blakiston Company, Philadelphia Price, \$3.50

Fundamentals of Psychiatry By EDWARD A STRECKER, M D, Sc D, F A C P 201 pages, 19.5 × 13 cm 1942 J B Lippincott Company, Philadelphia Price, \$3.00

Love Against Hate By KARL MENNINGER, M D 311 pages, 22 × 15 cm 1942 Harcourt, Brace and Company, New York Price, \$3.50

Biological Symposia, Vol IX Sex Hormones Edited by F C KOCH AND PHILIP E SMITH 146 pages, 25 × 17.5 cm 1942 The Jaques Cattell Press, Lancaster, Pennsylvania Price, \$2.50

Public Health and Preventive Medicine 2 volumes By MORTON C KAHN, M A, Ph D, D Sc 534 pages, 22 × 14 cm (each volume) 1942 Oxford University Press, New York Price, \$4.00 the set

Diseases of the Gastro-Intestinal Tract By ASHER WINKELSTEIN, M D, B S 195 pages, 22 × 14 cm 1942 Oxford University Press, New York Price, \$2.00

Urology By WILLIAM H MENCHER, A B, M D, F A C S 204 pages, 22 × 14 cm 1942 Oxford University Press, New York Price, \$2.00

Gynecologic Surgery By MORRIS A GOLDBERGER, M D, F A C S 164 pages, 22 × 14 cm 1942 Oxford University Press, New York Price, \$2.00

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

In previous issues of this journal, the names of 1,065 members of the College serving in the armed forces of their country were recorded. Herewith are reported the names of 57 additional members bringing the grand total to 1,122.

F Dennette Adams
 Ruel L Alden
 Samuel S Altshuler
 Benjamin M Baker, Jr
 Raymond L Barrett
 Carl B Beeman
 James B Berardi
 Gerald Blankfort
 Charles M Caravati
 Julius Chasnoff
 John B D'Albora
 George P Denny
 Richard D Evans
 Milton B Filberbaum
 Ralph L Fitts
 Paul D Foster
 Aime N Fregeau
 Franklin W Fry
 Irving Greenfield
 T Haynes Harvill
 Kendall B Holmes
 John A Hookey, Sr
 Sidney W Jennes
 James P Jordan
 Roger H Keane
 Bruce D Kenamore
 *Edwin P Kolb
 Samuel I Kooperstein
 Louis A M Krause

William A Lange
 Clarence W LeDoux
 John E Manley
 John B McKee
 James H McNeill
 Edgar M McPeak
 Ferrall H Moore
 Harold W Palmer
 Martin Patmos
 Richard O Pfaff
 Russell C Pigford
 Milton M Portis
 H William Primakoff
 Clark P Pritchett
 Norman Reider
 Howard A Rusk
 John B Schwedel
 John W Shadle
 Emil M Shebesta
 Ralph E Swope
 Milo K Tedstrom
 Martin V B Teem
 Edward G Thorp
 T Lloyd Tyson
 Lee D van Antwerp
 Norton W Voorhies
 Joseph O Weilbaecher, Jr
 Udo J Wile

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows

AMERICAN BOARD OF INTERNAL MEDICINE

William A Werrell, M D, Assistant Secretary
 1301 University Ave
 Madison, Wis

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

C Guy Lane, M D, Secretary
 416 Marlboro St
 Boston, Mass

* Retired to inactive duty

Written Examinations Will be given in various cities and at a number of Army and Naval stations, February 15, 1943

Oral Examinations Dates and place will be announced later

Written Examinations Will be given in various centers during October, 1943

Oral Examinations Philadelphia, Pa, December 3-4, 1943

AMERICAN BOARD OF PATHOLOGY
F W Hartman, M D, Secretary
Henry Ford Hospital
Detroit, Mich

AMERICAN BOARD OF PEDIATRICS
C A Aldrich, M D, Secretary
707 Fullerton Ave
Chicago, Ill

AMERICAN BOARD OF PSYCHIATRY AND
NEUROLOGY
Walter Freeman, M D, Secretary
1028 Connecticut Ave, N W
Washington, D C

AMERICAN BOARD OF RADIOLOGY
B R Kirklin, M D, Secretary
Mayo Clinic
Rochester, Minn

Written and Oral Examinations Spring, 1943, probably in connection with the meeting of the American Association of Pathologists and Bacteriologists, Chicago, Ill, April 1-2, 1943

Written Examinations Will be given in various centers, February 12, 1943

Oral Examinations St Louis, Mo, March 27-28, 1943 (closed), New York, N Y, April 24-25, 1943 (closed)

Oral Examinations Detroit, Mich, April, 1943, in advance of the meeting of the American Psychiatric Association Applications must be filed before March 1, 1943

Oral Examinations Spring and Fall, 1943, dates and place yet to be announced

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

- James E Ash, F A C P, Colonel, (MC), U S Army—"Atlas of Dental and Oral Pathology," "Atlas of Ophthalmic Pathology" and "Atlas of Otolaryngic Pathology",
Dr Harry R Litchfield, F A C P, Brooklyn, N Y—"Therapeutics of Infancy and Childhood," Vols II and III,
Dr Malcolm T MacEachern, F A C P, Chicago, Ill—"Hospital Organization and Management" and "Manual on Obstetric Practice in Hospitals",
Dr Francis M Pottenger, Jr, F A C P, Monrovia, Calif—"History of Randleigh Farm"

Reprints

- J Edward Berk, F A C P, Captain, (MC), U S Army—1 reprint,
Dr Nathan Blumberg, F A C P, Philadelphia, Pa,—2 reprints,
Dr Verne S Caviness, F A C P, Raleigh, N C—2 reprints,
Dr Nathan W Chaikin (Associate), New York, N Y—1 reprint,
Dr William Dameshek, F A C P, Boston, Mass—1 reprint,
Dr James M Flynn, F A C P, Rochester, N Y—1 reprint,
Dr Hugh Jeter, F A C P, Oklahoma City, Okla—1 reprint,
Dr Richard D Kepner, F A C P, Honolulu, T H—2 reprints,
Dr Harry D Leinoff (Associate), New York, N Y—2 reprints,
Dr William H Marshall, F A C P, Flint, Mich—1 reprint,
Horace P Marvin, F A C P, Lieutenant Colonel, (MC), U S Army—1 reprint,
Robert B Radl, F A C P, Major, (MC), U S. Army—1 reprint,
Dr Harry B Thomas, F A C P, York, Pa—1 reprint,
Dr Howard Wakefield, F A C P., Chicago, Ill—1 reprint,
Leon H Warren (Associate), Major, (MC), U S Army—3 reprints,

Dr William A Winn (Associate), Springville, Calif —2 reprints,
Dr Edwin E Ziegler, F A C P , Bethlehem, Pa —1 reprint.

Sanford W French, F A C P , Colonel, (MC), U S Army, has donated a publication entitled "Report on Allergy Clinics in Fourth Service Command, from April 1 to October 1, 1942" to the College Library This report was prepared under the direction of Colonel French

Dr George R Herrmann, F A C P , Galveston, Tex , has donated a bound volume of reprints entitled "The Publications of George R Herrmann, M D , and Associates, 1928-1938 " to our Library

PRESENT A C P OFFICERS, REGENTS AND GOVERNORS WILL SERVE DURING WAR

Inasmuch as the By-laws of the American College of Physicians provide that all Officers, Regents and Governors (except in the case of vacancies due to death or resignation) shall be elected by the Fellows and Masters of the College at an Annual Business Meeting, and since the Annual Sessions have been cancelled for the duration of the war and it becomes, therefore, impractical and next to impossible to hold an Annual Business Meeting of the members, it is apparent that the present Officers, Regents and Governors must continue to serve until the provisions of the By-laws may be fulfilled

Announcement was received on December 11, 1942, that Dr Hugh J Morgan, F A C P , Regent of the College, had been promoted from Colonel to Brigadier General in the Medical Corps of the U S Army, and is attached to the Office of the Surgeon General in Washington, D C

Dr Clifford W Mack, F A C P , Livermore, Calif , has been elected President of the Alameda County Medical Association

Dr Edwin E Ziegler, F A C P , Bethlehem, Pa , has resigned from the U S Public Health Service and has assumed the duties of Pathologist at St Luke's Hospital, Bethlehem

Dr Herbert T Kelly, F A C P , Philadelphia, Pa , spoke on "Medical Aspects of Nutrition" at a meeting of the Berks County (Pa) Medical Society, Reading, November 10, 1942

Dr Paul F Whitaker, F A C P , Kinston, N C , has resumed a limited consulting practice in Kinston with offices in the Memorial General Hospital

At a recent meeting of the Mississippi Valley Medical Editors' Association, Dr Harold Swanberg, F A C P , Quincy, Ill , was reelected Secretary and Dr George B Lake (Associate), Waukegan, Ill , was named a member of the Executive Committee

The 10th Annual Assembly of the Omaha Mid-West Clinical Society was held in Omaha, Nebr , on October 26-30, 1942 This meeting consisted of general assemblies, clinics, lectures and scientific and technical exhibits Among the distinguished guests at this meeting were

- Dr Russell L Haden, F A C P, Cleveland, Ohio—"Leukemia," "Undulant Fever",
 Dr. Herman H Riecker, F A C P, Ann Arbor, Mich—"The Clinical Anticipation of Disease," "Essential Hypertension",
 Dr Francis E Seneat, F A C P, Chicago, Ill—"Fungous Infections of the Skin," "New Drugs Used in Dermatology",
 Dr. Elmer L Sevringhaus, F A C P, Madison, Wis—"Diagnostic and Therapeutic Problems of the Menopause," "Use of Pituitary and Ovarian Therapy, Disturbances of Menstrual Rhythm and Fertility",
 Dr. Irvine H Page (Associate), Indianapolis, Ind—"Background for Modern Concepts of the Experimental Treatment of Hypertension," "Medical and Surgical Management of Hypertension"

Among the local Fellows of the College who participated in the program were

- Dr Lynn T Hall, F A C P—"The Present Status of Liver Tests",
 Dr Maurice C Howard, F A C P—"Management of Gastric Hemorrhage";
 Dr Ernest Kelley, F A C P—"Electric Shock in the Treatment of Psychoses",
 Dr Ernest L MacQuiddy, F A C P—"Oral Therapy in Hay Fever: A Review of Results in 1941 and 1942",
 Dr Frederick W Niehaus, F A C P—"Chest Pains Simulating an Anginal Syndrome",
 Dr Abraham S Rubnitz, F A C P—"Myocardial Changes Following Coronary Thrombosis",
 Dr Adolph Sachs, F A C P—"Renal Hypertension",
 Dr Warren Thompson, F A C P—"Hypothyroidism",
 Dr Edmond M Walsh, F A C P—"Management of Difficult Diabetics",
 Dr Harrison A Wigton, F A C P—"Intracranial Hemorrhage"

Among the Omaha members of the College who presented scientific exhibits were

- Dr M William Barry, F A C P, and Dr Ben Slutzky (Associate)—"Carotid Sinus Syndrome",
 Dr F Lowell Dunn, F A C P—"Cathode Ray Visualization of Lung and Heart Sounds",
 Dr Adolph Sachs, F A C P, and Dr Ben Slutzky (Associate)—"The Electrocardiophonograph—Heart Sounds",
 Dr Albert F Tyler, F A C P—"Radiation Therapy of the Breast," "Diseases of the Lungs and Mediastinum in Childhood"

Dr Russell L Haden conducted a clinic on "Menopausal Arthralgia, Infectious Arthritis, Gout Complicated by Hypertrophic Arthritis," Dr Francis E Seneat, a clinic on "Dermatology," and Dr Elmer L Sevringhaus, a clinic on "Postpartum Obesity with Menorrhagia and Sterility, Excessive Obesity with Menorrhagia, Obesity with Hypomenorrhea and Premenstrual Tension"

Dr W Warner Watkins, F A C P, Phoenix, Ariz, has resigned as Secretary of the Arizona State Medical Association and Dr Frank J Milloy, F A C P, Phoenix, has been named as his successor

On November 23, 1942, Dr Italo F. Volini, F A C P, Chicago, Ill, addressed the Chicago Society of Internal Medicine Dr Volini spoke on "Studies on Mercurial Diuresis Sudden Death Following Intravenous Injection, Report of Three Cases with Electrocardiographic Studies"

On the occasion of his seventieth birthday, Dr Emanuel Libman, F A C P , New York, N Y , was honored at a dinner at the Waldorf-Astoria, October 31, 1942 The dinner honoring Dr Libman was sponsored by the American Friends of the Hebrew University and the American Jewish Physicians Committee The speakers included Dr Joseph H Pratt, F A C P , Boston, Mass , and Leonard G Rowntree, F A C P , Colonel, (MC), U S Army

Dr John B Youmans, F A C P , Nashville, Tenn, Dr Udo J Wile, F A C P , U S Public Health Service, and Dr Reginald Fitz, F A C P , Boston, Mass , were among those who conducted a postgraduate refresher course sponsored by the Alumni Association of the Medical College of the State of South Carolina in Charleston, November 4-5, 1942

Dr Howard T Karsner, F A C P , Cleveland, Ohio, spoke on "Aortic Stenosis" at the Founders' Day Banquet of the Association

Dr Louis N Katz, F A C P , Chicago, Ill , will conduct a course in "Electrocardiographic Interpretation" at the Michael Reese Hospital, Chicago, beginning February 17, 1943 The class will meet once each week for a period of twelve weeks

Dr Herbert R Edwards, F A C P , New York, N Y , David Ulmai, F A C P , Lieutenant Commander, (MC), U S Navy, and Dr Edgar Mayer, F A C P , New York, N Y , were among those who conducted a clinical session on "Chronic Pulmonary Diseases" sponsored by the Tuberculosis Sanatorium Conference of Metropolitan New York, December 9, 1942

Dr Irvine H Page (Associate), Indianapolis, Ind , gave the Walter L Niles Memorial Lecture sponsored by Nu Sigma Nu at Cornell University Medical College, October 20, 1942 Dr Page spoke on "The Modern Concept of Hypertension "

Dr Oswald F Hedley, F A C P , U S Public Health Service, Bethesda, Md , discussed "The Cardiac in Industry" at a meeting of the New York Heart Association, December 1, 1942

Ursinus College Collegeville, Pa , has named its new science building the "Pfahler Hall of Science" in honor of Dr George E Pfahler, F A C P , Philadelphia, Pa Dr Pfahler has been a member of the Board of Directors of Ursinus College since 1935 and has been Professor of Radiology at the University of Pennsylvania School of Medicine, Philadelphia, since 1916

On October 30, 1942, Dr Byrl R Kirklın, F A C P , Rochester, Minn , spoke on "The Value of the Roentgen Rays to Diagnosis as It Pertains to the Physician Doing General Work" at a medical conference sponsored by the Medical Replacement Training Center at Camp Barkeley, Tex

Dr Frederic M Hanes, F A C P , Florence McAlister Professor of Medicine at Duke University College of Medicine, Durham, N C , was recently appointed Director of the Durham Emergency Base Hospital Unit, which has been established for the protection of the civilian population during the war.

The Fifth District Medical Society of Georgia held a semiannual meeting in Atlanta, October 19, 1942. Among the speakers were

Donald T. Chamberlin (Associate), Major, (MC), U. S. Army,—“Functional Digestive Diseases as Encountered at the Lawson General Hospital”,
Walter M. Bartlett, F. A. C. P., Major, (MC), U. S. Army,—“Three Thousand Hours of Cardiovascular Diseases in a General Hospital”

Dr. Lawrence Reynolds, F. A. C. P., Detroit, Mich., delivered the second Henry K. Pancoast Memorial Lecture before the Philadelphia Roentgen Ray Society and the Philadelphia College of Physicians on November 5, 1942. Dr. Reynolds spoke on “Newer Investigations of Radiation Effects and Their Clinical Application”

At the recent fall meeting of the Society for the Study of Asthma and Allied Conditions in New York, N. Y., Dr. John A. Kolmer, F. A. C. P., Philadelphia, Pa., spoke on “Biotherapy and Chemotherapy of the Respiratory Tract Diseases,” Dr. Milton B. Cohen, F. A. C. P., Cleveland, Ohio, on “Preliminary Report on the Fractionation of Ragweed Pollen and Immunological Studies with These Fractions,” and Dr. Abner M. Fuchs (Associate), New York, N. Y., on “The Treatment of Hay Fever with Gelatin Pollen Extracts”

At the annual session of the Association of American Medical Colleges held in Louisville, Ky., October 28, 1942, Dr. Waller S. Leathers, F. A. C. P., Nashville, Tenn., was installed as President and Dr. John Walker Moore, F. A. C. P., Louisville, was chosen Vice President

The 28th Annual Meeting of the Radiological Society of North America was held in Chicago, Ill., November 30–December 4, 1942. Among the speakers were

Dr. Benjamin H. Orndoff, F. A. C. P., Chicago, “Roentgen Castration for Malignant and Nonmalignant Diseases”,
Dr. Albert Soiland, F. A. C. P., Los Angeles, Calif.—“Plastic Induration of the Penis”

The Royal College of Physicians in Edinburgh has awarded its Cullen Prize to Dr. Thomas Addis, F. A. C. P., Professor of Medicine at Stanford University School of Medicine, San Francisco, Calif., for “the greatest benefit done to practical medicine in the last four years”. The research work of Dr. Addis included extensive study on the kidney

Dr. Andrew C. Ivy, F. A. C. P., who was recently appointed Chief Scientific Director of the new U. S. Naval Medical Research Institute in Bethesda, Md., delivered the fourteenth annual William T. Belfield Memorial Lecture at a meeting of the Chicago Urological Society, November 19, 1942. The subject of Dr. Ivy's lecture was “The Physiology of the Urinary Bladder, with Special Reference to Its Nerve Supply”

At the twenty-seventh Annual Dinner of the Institute of Medicine of Chicago, December 2, 1942, Dr. James B. Herrick, M. A. C. P., was honored for his many years of service to the Institute. Dr. Herrick was one of the founders of the Institute of Medicine. During 1925 he served as President of the Institute and he has been an active member of the Board of Governors since 1915.

The New York Academy of Medicine and the New York Heart Association are cooperating in a series of lectures on "Cardiovascular Diseases" Among those who will participate in these lectures are

- January 27, 1943—Dr Edwin P Maynard, Jr F A C P, Brooklyn N Y—"The Management of Cardiovascular Syphilis".
 March 24 1943—Irring S Wright, F A C P, Lieutenant Colonel, (MC), U S Army—"The Management of Peripheral Vascular Disease".
 April 28, 1943—Dr. Currier McEwen, F A C P, New York, N Y—"The Management of Rheumatic Fever".
 May 26, 1943—Dr Arthur C De Gaff, F A C P, New York, N Y—"The Management of Cardiac Arrhythmias".

Dr Israel Davidsohn, F A C P, Chicago, Ill, has been named Editor-in-Chief of the American Journal of Clinical Pathology

Dr Victor F Cullen, F A C P, State Sanatorium, Md, has been elected President of the Southern Tuberculosis Conference

At the annual meeting of the Central Society for Clinical Research held in Chicago, Ill, November 6-7, 1942, Dr John Walker Moore, F A C P, Louisville, Ky, was elected President Dr Cecil J Watson, F A C P, Minneapolis, Minn, was named Vice President and Dr Carl V Moore, F A C P, St Louis, Mo, Secretary-Treasurer

The Dallas Southern Clinical Society has cancelled its 1943 Spring Clinical Conference because of the national emergency

Dr Robert U Patterson, F A C P, at one time Surgeon General of the U S Army, and for the last several years Dean of the University of Oklahoma School of Medicine, has recently accepted the Deanship of the University of Maryland School of Medicine, Baltimore

DR EDWIN G BANNICK APPOINTED ACTING GOVERNOR FOR WASHINGTON

The Executive Committee of the Board of Regents of the College recently appointed Dr Edwin G Bannick, F A C P, Medical and Dental Bldg, Seattle, Wash, Acting Governor for the State of Washington, during the absence of Dr Charles E Watts, who is serving as Commander in the Medical Corps of the U S Navy on duty in the Pacific

REGIONAL MEETING AND "POSTGRADUATE NIGHTS" HELD IN CHICAGO AREA

The American College of Physicians conducted "Postgraduate Nights" programs, November 19-20, and held a Regional Meeting, including the States of Illinois, Indiana, Iowa, Michigan and Wisconsin, at the Drake Hotel, Chicago, on November 21 At the "Postgraduate Nights" meeting at Camp Grant, Ill, there were in attendance somewhat over two hundred Medical Officers of the Army, with a few Medical Officers in attendance from the Navy At the program at the Great Lakes Naval Hospital approximately two hundred Medical Officers of the Navy and a few Medical Officers from the Army were in attendance Both programs were received with enthusiasm and appreciation

The Regional Meeting in Chicago was the first real attempt to combine several States Twenty-five per cent (25%) of the Fellows and Associates of the College located in the States represented were in attendance An analysis of attendance is as follows :

	Master	Fellows	Associates	Guests	TOTAL	Civilian Doctors	Service Doctors
Illinois	1	60	24	89	174	130	44
Indiana		10	2	2	14	12	2
Iowa		8	1		9	9	
Michigan		19	12	6	37	25	12
Wisconsin		10	5	4	19	12	7
Miscellaneous							
District of Columbia		1		1	2		2
Georgia		1			1	1	
Kentucky				1	1		1
Maryland		1			1		1
Massachusetts		1			1	1	
Minnesota		1			1	1	
Missouri				1	1		1
Oklahoma		1			1	1	
Pennsylvania				1	1		
Ontario, Canada				1	1		1
	1	113	44	106	264*	193	71

* If we add to this total at the Regional Meeting approximately four hundred additional service physicians who attended the "Postgraduate Nights" program, it makes a grand total of 664

The programs were as follows

Postgraduate Nights

Thursday, November 19, 1942

OFFICERS CLUB

CAMP GRANT, ILLINOIS

8 00 P M

Presiding Officer

JOHN M WILLIS, M D , F A C P
Brigadier General, M C , U S Army
Commanding General, Camp Grant

- 1 "Shock " Warren H Cole, M D , F A C S (by invitation), Professor of Surgery and Head of the Department of Surgery, University of Illinois College of Medicine, Chicago, Ill
- 2 "Pre-operative Preparation of Patients " Robert W Keeton, M D , F A C P , Professor of Medicine and Head of the Department of Internal Medicine, University of Illinois College of Medicine, Chicago, Ill
- 3 "Penetrating Injuries of the Chest " Willard Van Hazel, M D , F A C S (by invitation), Professor of Surgery, University of Illinois College of Medicine, Chicago, Ill
- 4 "Atypical (Virus ?) Pneumonia " Clayton Loosli, M D (by invitation), Assistant Professor of Medicine, University of Chicago, Chicago, Ill

Friday, November 20, 1942

GREAT LAKES NAVAL HOSPITAL

GREAT LAKES, ILLINOIS

8 00 P M

Presiding Officer

WILLIAM E. EATON, M D, F A C S

Captain, M C, U S Navy

Commanding Officer, Great Lakes Naval Hospital

- 1 "35 mm Photofluorography as Used in the Navy" Robert E. Duncan, M D, F A C P (by appointment), Captain, M C, U S Navy, Executive Officer, U S Naval Hospital, National Naval Medical Center, Bethesda, Md
- 2 "Syphilitic Heart Disease" James E. Paullin, M D, F A C P, President, American College of Physicians, President-Elect, American Medical Association, Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Ga
- 3 "Clinical Signs of Nerve Regeneration" Lewis J. Pollock, M D (by invitation), Professor and Head of the Department of Nervous and Mental Diseases, Northwestern University Medical School, Chicago, Ill
- 4 "Recent Advances in the Treatment of Infectious Diseases" Archibald L. Hoyne, M D, F A C P, Professor of Pediatrics, University of Chicago, Director and Chief of the Department of Contagious Diseases, Cook County Hospital and the Municipal Contagious Hospital, Chicago, Ill

Regional Meeting

LEROY H. SLOAN, M D, F A C P

Governor for Northern Illinois

WILLARD O. THOMPSON, M D, F A C P

Chairman, Program and Arrangements Committee

Chicago

Saturday, November 21, 1942

MORNING SESSION—9 00 A M

- "The Treatment of Arterial Hypertension with Ascorbic Acid" Nathan S. Davis, III, M D, F A C P, Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill
- "Nutritional Problems in War Time" Clifford J. Barborika, M D, F A C P, Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill
- "The Effect of Altitude on Peripheral Circulation" Carl Johnson, M D (by invitation), A. Wilson Smith, M D (by invitation) and Thomas J. Coogan, M D, F A C P, St. Luke's Hospital, Chicago, Ill
- "Significance of Joint Pains Caused by Sterile Streptococcus Toxin" Paul S. Rhoads, M D, F A C P, Associate Professor of Medicine, and Melvin E. Afremow, M D (by invitation), Northwestern University Medical School and Cook County Hospital, Chicago, Ill
- "Maintaining High Standards of Medical Practice with Decreasing Personnel" Roscoe L. Sensenich, M D, F A C P, Board of Trustees, American Medical Association, South Bend, Ind

- "Acute Nephritis and the Effect of Sulphonamides on the Kidney" Francis D Murphy, M D, F A C P, Professor of Medicine and Head of the Department, Marquette University School of Medicine, Milwaukee, Wis
- "Persistence of Estrogen Induced Sexual Development" Henry H Turner, M D, F A C P, Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla
- "Army Casualties—Honolulu, December 7, 1941" T Donald McCarthy, M D. (by invitation), Major, Medical Corps, U S Army. Camp Grant, Ill

Intermission

- "Psychoneuroses in War Time" Lloyd H Ziegler, M D (by invitation), Professor of Psychiatry, University of Illinois College of Medicine, Director, Milwaukee Sanitarium, Wauwatosa, Wis
- "Bronchoscopic Observations in Atypical Pneumonia" Paul H Holinger, M D, F A C S (by invitation), Director, Department of Peroral Endoscopy, St Luke's Hospital, and University of Illinois College of Medicine, Chicago, Ill
- "Recent Advances in the Treatment of Contagious Diseases" Archibald L Hoyne, M D, F A C P, Chief, Contagious Disease Department, Cook County Hospital and Municipal Contagious Hospital, Chicago, Ill
- "Physical Therapy in Civilian Defense" John S Coulter, M D, F A C S (by invitation), Regional Medical Officer, 6th Civilian Defense Region, Chicago, Ill
- "Gastro-intestinal Disorders in the Armed Forces" Ralph C Brown, M D (by invitation), Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill
- "Aspiration Pneumonia" Carl W Apfelbach, M D (by invitation), Professor of Pathology, and Ernest E Irons, M D, F A C P, Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill

AFTERNOON SESSION—2 00 P M

Ballroom, Drake Hotel

- "Rifles on the Firing Line" Charles C Hillman, M D, F A C P, Brigadier General, Medical Corps, U S Army, Chief of Professional Service Division, Office of the Surgeon General, Washington, D C
- "Syphilitic Heart Disease" James E Paulin, M D, F A C P, President, American College of Physicians, President-Elect, American Medical Association, Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Ga
- "Aviation Medicine" Walter M Boothby, M D, F A C P, Chairman, Mayo Aero Medical Unit, Rochester, Minn
- "The Problems of the Internist in the Navy" Robert E Duncan, M D, F A C P (by appointment), Captain, Medical Corps, U S Navy, Executive Officer, U S Naval Hospital, National Naval Medical Center, Bethesda, Md

Intermission

- "Medical Care of Aviation Personnel" David N W Giant, Brigadier General, Air Surgeon, Army Air Force, Washington, D C
- "Cardiac Problems in War Time" Paul D White, M D, F A C P, Physician, Massachusetts General Hospital, and Lecturer, Harvard Medical School, Boston, Mass
- "Shock" Warren H Cole, M D, F A C S (by invitation), Professor of Surgery and Head of the Department University of Illinois College of Medicine, Chicago, Ill

"Present Emergency " Frank V Meriwether, M D (by appointment), Senior Surgeon, Director, U S Public Health Service, District No 3, Chicago, Ill

The Afternoon Session was followed by a social hour and cocktails in the Gold Coast Room of the Drake Hotel, followed by an informal dinner, at which Dr LeRoy H Sloan acted as Toastmaster Brief addresses were made by Brigadier General C C Hillman (MC), U S Army, official envoy from the Office of the Surgeon General, Brigadier General David N W Grant, Air Surgeon of the U S Army Air Force, Washington, D C , Captain Robert E Duncan (MC), U S Navy, official envoy of the Surgeon General of the Navy, Dr Frank V Meriwether, Senior Surgeon, U S Public Health Service, official envoy of the Surgeon General of that Service, Dr James E Paullin, Atlanta, Ga , President of the College, Dr Ernest E Irons, Chicago, President-Elect of the College, and Brigadier General John M Willis (MC), U S Army, Commanding Officer, Camp Grant, Ill Dr Morris Fishbein, Editor of the Journal of the American Medical Association, made the principal address Among distinguished guests introduced by the Toastmaster were Dr Cecil M Jack, Decatur, A C P Governor for southern Illinois, Dr Robert M Moore, Indianapolis, A C P Governor for Indiana, Dr B F Wolverton, Cedar Rapids, A C P Governor for Iowa, Colonel Henry R Carstens (MC), U S Army, A C P Governor for Michigan, Dr P L Ledwidge, Detroit, A C P Acting Governor for Michigan, Dr Elmer L Sevringhaus, Madison, A C P Governor for Wisconsin, Colonel Walter B Martin (MC), U S Army, A C P Governor for Virginia, Mr E R Loveland, Philadelphia, Executive Secretary of the College, Captain Henry L Dollard (MC), U S Navy, Commanding, Ninth Naval District, Great Lakes, Ill , Captain William E Eaton (MC), U S Navy, Commanding Officer, Great Lakes Naval Hospital, Dr Paul D White, Boston, Dr Walter M Boothby, Rochester, Minn , Dr Arthur R Elliott, Chicago, former Regent of the College, Dr James P Simonds, Acting President of the Chicago Medical Society, Dr Wilber E Post, President, Chicago Institute of Medicine, Dr Charles Phifer, Director, Office of Procurement and Assignment, Sixth Service Command, Chicago, Dr Roscoe L Sensenich, South Bend, Ind , Trustee of the American Medical Association, Dr Malcolm T MacEachern, Chicago, Associate Director of the American College of Surgeons, Dr D J Davis, Dean, University of Illinois College of Medicine, Dr J Roscoe Miller, Dean, Northwestern University Medical School, and Dr J G Powers, Acting Dean, Loyola University School of Medicine

SPECIAL NOTICES

OFFICE OF WAR INFORMATION

WAR PRODUCTION BOARD

Additional control over the purchase of laboratory equipment was put into effect by the issuance on December 5, 1942 of Limitation Order L-144, as amended

The amended order provides that no purchaser of laboratory equipment shall be permitted to acquire an item valued at more than \$50 or any quantity of the same item to the value of more than \$50, without securing an authorization for such purchase from the Director General for Operations

Application should be made on Form PD-620 Purchases authorized on the basis of this form will be assigned an AA-4 rating

"Laboratory equipment" is defined in the order to mean material, instruments, appliances, devices, parts thereof, tools and operating supplies for laboratories, or for use in connection with operations usually carried on in laboratories, not including second-hand items

THE AMERICAN SOCIAL HYGIENE ASSOCIATION, INC

1790 BROADWAY, NEW YORK, N Y

Social Hygiene Day will take its battle stations throughout the country as in former years, despite the gasoline and rubber restrictions which are in force this year. Dr. Walter Clarke, Executive Director of the American Social Hygiene Association, in announcing the annual observance scheduled for Wednesday, February 3, 1943, said that this battle on the home front against venereal disease is nationwide and does not depend upon transportation to rally its fighting forces. Community meetings will take place throughout the land, sponsored by local clubs, church groups, and social and health agencies.

Last year, when tires and gas were not restricted, Social Hygiene Day was observed by thousands of public meetings, held in communities all over the United States, Dr. Clarke explained. He intimated that this number promises to be greatly increased in 1943, for the large meetings, serving metropolitan areas, will be supplemented by an even greater number of local meetings.

Dr. Clarke pointed out that in wartime more than ever the United States must man its battle stations in every city, town and hamlet, in order to stamp out the venereal diseases at their source. Syphilis and gonorrhea are enemies which threaten us at home. They disable our men at the front, but their roots are on the home front. For this reason Social Hygiene Day this year will assume a greater significance than ever before. It will be observed in every community, no matter how small it may be, by discussion of direct action designed to stamp out the two diseases which are as menacing to our armed forces as the bombs of our enemies.

"During the first world war, there were 157,146 more new cases of syphilis and gonorrhea among United States soldiers, sailors and marines," Dr. Clarke explained, "than there were wounds in battles. Total absences from duty due to this infection kept the equivalent of 20,600 men out of the fighting for a whole year, men trained for their country's service, men upon whom their country counted for its defense."

"In terms of today's hard held fronts such a loss would mean the equivalent of the personnel required to man five huge aircraft carriers and nine destroyers. No axis enemy could be more destructive than this enemy whom we must defeat on health battle fronts within our own country. We do not need to suffer this loss and do not need gas and tires to meet that enemy and to destroy him. We have the scientific weapons to prevent the spread of the venereal diseases. In war time the principal function of social hygiene organizations everywhere is to persuade every community to use these weapons effectively. Intelligent cooperation among the health and welfare agencies in every city and town will help stamp out venereal disease and thus help our armed forces to bring us victory on the battle fronts."

POSTGRADUATE COURSE IN INDUSTRIAL MEDICINE AND HYGIENE OFFERED
IN PHILADELPHIA

Under the auspices of The Philadelphia County Medical Society, directed by the Departments of Preventive Medicine and Public Health of the University of Pennsylvania and the Woman's Medical College of Pennsylvania, a Postgraduate Course in Industrial Medicine and Hygiene will be offered in Philadelphia for a period of eight weeks, beginning the first week in January. The classes will meet from 4 00 to 6 00 p m on Tuesdays, Thursdays and Saturdays, and the course will extensively cover the field. Copies of the program may be obtained by communicating directly with The Philadelphia County Medical Society.

FRIDAY AFTERNOON LECTURE SERIES—1942-43

At 4 30 o'clock

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street, New York City

1942

- November 6 Disorders of the hypophysis from a clinical standpoint David P Barr, Professor of Medicine, Cornell Univ Medical College
- November 13 Some recent advances in therapeutics, including the newer drugs of the sulfonamide group Harry Gold, Assistant Professor, Department of Pharmacology, Cornell University Medical College
- November 20 The surgical treatment of circulatory disorders in the lower extremities, including diabetic gangrene Gerald H Pratt, Assistant Clinical Professor of Surgery, New York Post-Graduate Medical School, Columbia University
- December 4 The rôle of artificial insemination in treating human sterility Alan F Guttmacher, Associate Professor of Obstetrics, Johns Hopkins Medical School, Baltimore
- December 11 Virus pneumonia Hobart A Reimann, Professor of Medicine, Jefferson Medical College, Philadelphia
- December 18 Peritonitis, conservative treatment Henry W Cave, Assistant Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University

1943

- January 8 Present concepts and treatment of sinusitis Russell C Grove, Associate Otolaryngologist, Roosevelt Hospital
- January 15 Shoulder pain and disabilities David M Bosworth, Associate Attending Orthopedic Surgeon, St Luke's Hospital
- January 22 Indications and contraindications for the newer anesthetic agents Milton C Peterson, Associate Professor of Anesthesia, New York Post-Graduate Medical School, Columbia University
- January 29 Modern treatment of the psychoses S Bernard Wortis, Professor of Psychiatry, New York University Medical College
- February 5 Intractable pain—surgical and medical treatment Byron Stookey, Professor of Clinical Neurological Surgery, College of Physicians and Surgeons, Columbia University
- February 19 Clinical types of coronary insufficiency and their recognition Robert L Levy, Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University
- February 26 Recent advances in the clinical interpretation of laboratory data Maurice Bruger, Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University
- March 5 The rôle of the RH factor in erythroblastosis, transfusion accidents, and its importance to the obstetrician Philip Levine, Bacteriologist to the Newark Beth Israel Hospital, Newark
- March 12 Toxemias of pregnancy Albert H Aldridge, Chief Surgeon, Woman's Hospital
- March 19 Brucellosis diagnosis, differential diagnosis and treatment Harold J Harris, Lieut Commander, (MC) USNR
- March 26 Rheumatoid arthritis and its treatment, including gold therapy M Henry Dawson, Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University

- April 2 Postcholecystectomy syndrome Ralph Colp, Clinical Professor of Surgery,
College of Physicians and Surgeons, Columbia University
- April 9: Phosphatase values in relation to bone diseases Henry L. Jaffe, Director of
Laboratories, Hospital for Joint Diseases
- April 16: Value of roentgen therapy in inflammatory conditions Maurice Lenz, Pro-
fessor of Clinical Radiology, College of Physicians and Surgeons, Columbia
University
-

NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 13, 1942, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated

ELECTIONS TO FELLOWSHIP

December 13, 1942

Fellowship Candidates

Sponsors

ARIZONA

Leslie Rest Kober, Phoenix
Hilton John McKeown, Phoenix

Howell Randolph, Earle W. Phillips, Fred G. Holmes
Robert S. Flinn, Frank J. Milloy, Fred G. Holmes

ARKANSAS

John Nye Compton, Little Rock

Silas C. Fulmer, Paul C. Eschweiler, Oliver C. Melson

CALIFORNIA

Kendall Bennett Holmes, Fresno
Walter Charles Smallwood, Long Beach
Francis Marion Pottenger, Jr., Monrovia
Edward Carl Rosenow, Jr., Pasadena

W. E. Richard Schottstaedt, Ernest B. Bradley,
Ernest H. Falconer
Burrell O. Raulston, Howard F. West, Roy E. Thomas
Willard J. Stone, Egerton L. Crispin, Roy E. Thomas
Willard J. Stone, Burrell O. Raulston, Roy E. Thomas

COLORADO

Clarke Horace Barnacle, Denver
(M R C, U S A)
Robert Todd Terry, Denver
(M R C, U S A)

Ward Darley, Jr., Charles S. Bluemel, James J. Waring
W. Bernard Yegge, Ward Darley, Jr., James J. Waring

CONNECTICUT

Edward Gipstein, New London
William Harold Weidman, Norwich
James Roby Gudger, West Hartford
(M C, U S N R)

Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington
Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington
Alvin E. Murphy, Harold J. Stewart, Charles H. Turkington

DISTRICT OF COLUMBIA

General Profession

Harry Filmore Dowling, Washington

Walter K. Myers, George R. Minot, Wallace M. Yater

*Fellowship Candidates**Sponsors*

MEDICAL CORPS, U S NAVY

Ladislaus Louis Adamkiewicz, Portland, Maine	Donald H Daniels, Mortimer Warren, Ross T McIntire
Gordon Bennett Tayloe, Philadelphia, Pa	Ross T McIntire

U S PUBLIC HEALTH SERVICE

Mason Victor Hargett, Hamilton, Mont	Ferdinand R Schemm, Ernest D Hitchcock, Thomas Parran
Frederick Andrew Johansen, Carville, La	Thomas Parran

FLORIDA

Rollin David Thompson, Orlando	Meredith Mallory, Spencer A Folsom, Turner Z Cason
--------------------------------	---

GEORGIA

Arthur Park McGinty, Atlanta (M C, U S N R)	Evert A Bancker, Mason I Lowance, Glenville Giddings
--	---

ILLINOIS

Arthur Seldon Mann, Alton (M R C, U S A)	V Thomas Austin, Charles H Drenckhahn, Cecil M Jack
Richard Brooks Capps, Chicago (M R C, U S A)	George H Coleman, Fred E Ball, LeRoy H Sloan
Gilbert Henry Marquardt, Chicago	James G Carr, Alexander A Goldsmith, LeRoy H Sloan
Theodore Robert Van Dellen, Chicago (M R C, U S A)	J Roscoe Miller, James G Carr, LeRoy H Sloan
George Clarence Turnbull, Evanston (M R C, U S A)	Samuel J Lang, James G Carr, LeRoy H Sloan
Eugene Lawrence Walsh, Evanston (M R C, U S A)	J Roscoe Miller, Laurence E Hines, LeRoy H Sloan
John Edward McCorvie, Peoria	Harry A Durkin, George Parker, Cecil M Jack
William Joseph Bryan, Rockford	Henry C Sweany, Karl J Henrichsen, Cecil M Jack
Richard Fleetwood Herndon, Springfield	George B Stericker, Samuel E Munson, Cecil M Jack
Arthur Sterling Webb, Wheaton	Walter H Watterson, Josiah J Moore, LeRoy H Sloan

INDIANA

Arthur B Richter, Indianapolis	James O Ritchey, Edgar F Kiser, Robert M Moore
--------------------------------	---

IOWA

Willis Marion Fowler, Iowa City	Fred M Smith, John C Parsons, Benjamin F Wolverton
James Alexander Greene, Iowa City	Fred M Smith, John C Parsons, Benjamin F Wolverton
Horace Marshall Korns, Iowa City	Fred M Smith, John C Parsons, Benjamin F Wolverton

KANSAS

Clarence Wilber Erickson, Pittsburg (M R C, U S A)	Thomas T Holt, Fred J McEwen, Harold H Jones
---	---

LOUISIANA

Joseph Steven D'Antoni, New Orleans	John H Musser, Grace A Goldsmith, Joseph E Knighton
-------------------------------------	--

Fellowship Candidates

Chester Sebastian Fresh, New Orleans
(M R C., U S A)
Manuel Gardberg, New Orleans

Sponsors

Edgar Hull, Joseph O Weilbaecher, Jr, Joseph
E Knighton
Allan Eustis, Randolph Lyons, Joseph E
Knighton

MARYLAND

Charles Henry Conley, Jr, Buckeystown
(M C, U S N R)

Henry M Hensen, Sydney R Miller, Wether-
bee Fort

MASSACHUSETTS

Thomas Hale Ham, Boston

Lester Dow Watson, Milton

Allen Gilbert Brasley, Newton Highlands
(M C, U S N R)

Hugh Francis Folsom, Southborough

George R Minot, Chester S Keefer, William
B Breed

Chester S Keefer, John A Foley, William B
Breed

Greene FitzHugh, Maurice Fremont-Smith,
William B Breed

James H Means, Paul D White, William B
Breed

MICHIGAN

John McFarland Sheldon, Ann Arbor
(M R C, U S A)

Abraham Becker, Detroit
(M R C, U S A)

Nelson Wright Diebel, Detroit

Benjamin Juliar, Detroit
(M R C, U S A)

Mark Ronald McQuiggan, Detroit

Max Karl Newman, Detroit

Louis John Steiner, Detroit

Gordon Wesley Balyeat, Grand Rapids
(M C, U S N R)

Benjamin Bismark Blum, Petoskey

Cleo Russel Gatley, Pontiac
(M R C, U S A)

Evert Waitman Meredith, Port Huron

Bernard Alec Watson, Three Oaks
(M R C, U S A)

Cyrus C Sturgis, Herman H Riecker, Douglas
Donald

Solomon G Meyers, Douglas Donald, Patrick
L Ledwidge

George B Hoops, Rollin H Stevens, Henry R
Carstens

Emmet F Pearson, Gordon B Myers, Harry L
Arnold, Patrick L Ledwidge

Louis J Bailey, John A Hookey, Patrick L
Ledwidge

George B Hoops, Curt P Schneider, Patrick
L Ledwidge

Frank J Sladen, John G Mateet, Patrick L
Ledwidge

Joseph B Whinery, Sumner M Wells, Jr,
Patrick L Ledwidge

Edgar V Allen, Floyd H Lashmet, Douglas
Donald

Harold R Roehm, George A Sherman, Patrick
L Ledwidge

Frank J Sladen, F Janney Smith, Douglas
Donald

Martin A Mortensen, Lloyd E Verity, Cyrus
C Sturgis, Douglas Donald

MINNESOTA

Alphonse Edmund Walch, Minneapolis

Edwin L Gardner, Ragnvald S Ylvisaker, Ed-
ward H Rynearson

MISSOURI

Michael Bernreiter, Kansas City
(M R C, U S A)

Samuel H Snider, Frank I Ridge, A Comingo
Griffith

MONTANA

Charles Francis Little, Great Falls

Meredith Benjamin Hesdorffer, Missoula
(U S P H S, R)

Ferdinand R Schemm, Harold W Gregg,
Ernest D Hitchcock

Allen R Foss, Archie L Gleason, Ernest D
Hitchcock

NEBRASKA

Orange Van Calhoun, Lincoln

Floyd L Rogers, John C Thompson, Warren
Thompson

Fellowship Candidates

Frederick Hnat, Elizabeth
(MRC, USA)
Joseph Joel Labow, Elizabeth
Jesse McCall, Newton
(MRC, USA)

Benjamin Burbank, Brooklyn
(MRC, USA)
Louis Friedfeld, Brooklyn
(MRC, USA)
Irving Greenfield, Brooklyn
(MRC, USA)
Arthur Gerson Hollander, Brooklyn
(MRC, USA)
Aaron Arnold Karan, Brooklyn
Abraham M Litvak, Brooklyn
Samuel Millman, Brooklyn
(MRC, USA)
Abraham Max Rabiner, Brooklyn
Bernard Seligman, Brooklyn
John James Weber, Brooklyn
Edgar Coleman Beck, Buffalo
Walter David Westinghouse, Buffalo
George Miner Mackenzie, Cooperstown
Michael Bevilacqua, Glendale
(MRC, USA)
James Burnett Shields, Glens Falls
Henry Craig Fleming, New York
Herman Louis Frosch, New York
William Alden Gardner, New York
Samuel Waldron Lambert, Jr, New York
Mack Lipkin, New York
Aaron Edwin Margulis, New York
Carl Muschenheim, New York
Eli Hyman Rubin, New York
Gamlhel Saland, New York
Frederick William Williams, New York
John Winthrop Pennock, Syracuse, N Y
(MRC, USA)
Ranald Edwards Mussey, Troy
Harold Jerome Harris, Westport
(MC, USNR)

Sponsors

NEW JERSEY

Horace R Livengood, Michael Vinciguerra,
George H Lathrope
Arturo R Casilli, Harry Bloch, George H
Lathrope
George J Young, Harold S Hatch, George H
Lathrope

NEW YORK

J Hamilton Crawford, Tasker Howard, C F
Tenney
Charles Shookhoff, William Goldring, Asa L
Lincoln
Tasker Howard, Irving Gray, C F Tenney
J Hamilton Crawford, William H Lohman,
Asa L Lincoln
Morris M Banowitch, Isaac Gerber, Asa L
Lincoln
Maurice J Dattelbaum, Jean A Curran, C F
Tenney
Simon R Blatteis, Irving J Sands, Asa L
Lincoln
Orman C Perkins, Tasker Howard, Asa L
Lincoln
Henry M Feinblatt, Tasker Howard, C F
Tenney
Alexis T Mays, William A Lange, C F
Tenney
Allen A Jones, Abraham H Aaron, Nelson G
Russell
Stuart L Vaughan, Francis E Kenny, Nelson
G Russell
Robert F Loeb, Randolph West, Walter W
Palmer, C F Tenney
Frank R Mazzola, Goodwin A Distler, Asa L
Lincoln
Morris Maslon, George A Chapman, Asa L
Lincoln
Russell L Cecil, Arthur F Chace, Asa L
Lincoln
Nathan B Van Etten, Isidore W Held, C F
Tenney
Robert F Loeb, Randolph West, Walter W
Palmer, Asa L Lincoln
Robert F Loeb, Franklin M Hanger, Walter
W Palmer, C F Tenney
Walter G Lough, Carl H Greene, Asa L
Lincoln
Max Pinner, J Burns Amberson, Jr, C F
Tenney
Claude E Forkner, Harold G Wolff, Asa L
Lincoln
Max Pinner, David Marine, Asa L Lincoln
Irving J Sands, H Rawle Geyelin, Asa L
Lincoln
Herman O Mosenthal, James R Scott, Asa L
Lincoln
William A Groat, Edward C Reifenstein, Nel-
son G Russell
Stephen H Curtis, Crawford R Green, Asa L
Lincoln
Stanton Tice Allison, James L McCartney, Asa
L Lincoln

*Fellowship Candidates**Sponsors*

NORTH CAROLINA

Joseph John Combs, Raleigh
 Thomas Leonard Umphlet, Raleigh

Hubert B Haywood, William B Dewar, Paul
 F Whitaker
 Verne S Caviness, Hubert B Haywood, Paul
 F Whitaker

OHIO

Ellis Herndon Hudson, Athens
 (M C, U S N R)
 Sander Cohen, Cincinnati
 (M R C, U S A)
 Charles Kenneth Riddle, Cincinnati
 William Parrish Garver, Cleveland
 McKinley London, Cleveland
 (M C, U S N R)
 Mortimer Lee Siegel, Cleveland
 Francis Joseph Heringhaus, Mansfield
 (M R C, U S A)
 Raymond John Borer, Toledo
 (M R C, U S A)
 Charles Harry Warnock, Youngstown

Calvus E Richards, Charles A Doan, A B
 Brower
 Hiram B Weiss, Robert C Rothenberg, A. B
 Brower
 John H Skavlem, David A Tucker, Jr, A B
 Brower
 John A Toomey, Harold Feil, Ray W Kissane,
 A B Brower
 Vernon C Rowland, Charles T Way, A B
 Brower
 Samuel S Berger, Roy W Scott, A B Brower
 Roy W Scott, Theodore L Bliss, A B Brower
 Frank C Clifford, John T Murphy, A B
 Brower
 Colin R Clark, William H Bunn, A B Brower

OKLAHOMA

William Turner Bynum, Chickasha
 James Floyd Moorman, Oklahoma City

Philip M McNeill, Wann Langston, Lea A
 Riely
 Joseph T Martin, Hull W Butler, Lea A
 Riely

OREGON

Edmund Henry Berger, Portland
 (M C, U S N R)
 Donald Edgar Forster, Portland
 (M R C, U S A)
 Howard Phelps Lewis, Portland
 (M R C, U S A)

Marr Bisailon, John H Fitzgibbon, Homer P
 Rush
 Edwin E Osgood, David W E Baird, Homer
 P Rush
 John H Fitzgibbon, Marr Bisailon, Homer P
 Rush

PENNSYLVANIA

Allen Wilson Cowley, Harrisburg
 Harvey Holmes Seiple, Lancaster
 George Warren Burnett, Oil City
 Andrew Wirt Goodwin, Oil City
 Jack Edward Berk, Philadelphia
 (M R C, U S A)
 Julius Hiram Comroe, Jr, Philadelphia
 William Wallace Dyer, Philadelphia
 Kendall Adams Elsom, Philadelphia
 (M R C, U S A)
 John Quintin Griffith, Jr, Philadelphia
 John Day Garvin, Pittsburgh

Carl E Ervin, Charles C Wolferth, Edward L
 Bortz
 Roland N Klemmer, Samuel S Simons, Ed-
 ward L Bortz
 Kelse M Hoffman, Harvey M Watkins, R R
 Snowden
 Harvey M Watkins, C Howard Marcy, R R
 Snowden
 Henry L Bockus, Martin E Reh fuss, Edward
 L Bortz
 Simon S Leopold, T Grier Miller, Edward L
 Bortz
 Edward S Dillon, Thomas Fitz-Hugh, Jr, Ed-
 ward L Bortz
 T Grier Miller, Charles C Wolferth, O H
 Perry Pepper, Edward L Bortz
 Charles C Wolferth, T Grier Miller, Edward
 L Bortz
 George J Wright, C Howard Marcy, R R
 Snowden

SOUTH CAROLINA

Albert May Eaddy, Columbia

J Heyward Gibbes, Hugh Smith, Kenneth M
 Lynch

*Fellowship Candidates**Sponsors*

Bergein Marion Overholt, Knoxville
(M R C, U S A)

William Ladelle Howell, Fort Worth
(M R C, U S A)

Flavius Downs Mohle, Houston
(M R C, U S A)

Edwin G. Faber, Tyler
(M R C, U S A)

Emory Dallas Hollar, Vernon

Lloyd Lorenzo Cullimore, Provo

James Porter Baker, Richmond
(M R C, U S A)

Nathan Bloom, Richmond

Harold Julian Gunderson, Everett
(M R C, U S A)

Eric MacMillan Chew, Seattle
(M R C, U S A)

Clark Cleo Goss, Seattle
(M C, U S N R)

John Pierpont Helmick, Fairmont

Adolph Matthew Hutter, Fond du Lac

M Meredith Baumgartner, Janesville

Ruth Caldwell Foster, Madison

Edgar Stillwell Gordon, Madison
(M R C, U S A)

Ovid Otto Meyer, Madison

Kenneth Paul Hoel, Pewaukee

Harold Herman Fechtner, Wausau

Henry Costill Gotshalk, Honolulu

Harold Orr, Edmonton

Francis Alexander Lavens Mathewson,
Winnipeg (R C A F)

TENNESSEE

Daniel R. Thomas, Robert B. Wood, J. O.
Manier, William C. Chaney

TEXAS

Truman C. Terrell, May Owen, M. D. Levy

Alvis E. Greer, Henry N. Gemoets, M. D. Levy

H. Frank Carman, David W. Carter, Jr., M. D.
Levy

Truman C. Terrell, Oliver B. Kiel, M. D. Levy

UTAH

Ivan Thompson, Fuller B. Bailey, Louis E.
Viko

VIRGINIA

Douglas G. Chapman, T. Dewey Davis, Walter
B. Martin

Harry Walker, Douglas G. Chapman, Walter B.
Martin

WASHINGTON

George D. Capaccio, Lester J. Palmer, Edwin
G. Bannick

Lester J. Palmer, George D. Capaccio, Edwin
G. Bannick

James E. Hunter, Homer Wheelon, Edwin G.
Bannick

WEST VIRGINIA

Charles W. Waddell, J. Lewis Blanton, Albert
H. Hoge

WISCONSIN

Karver L. Puestow, Chester M. Kurtz, Elmer
L. Sevringhaus

Vincent W. Koch, Thomas O. Nuzum, Elmer
L. Sevringhaus

Chester M. Kurtz, Joseph S. Evans, Elmer L.
Sevringhaus

Joseph S. Evans, Marie L. Carns, Elmer L.
Sevringhaus

Joseph S. Evans, Harold M. Coon, Elmer L.
Sevringhaus

Harold M. Coon, Llewellyn R. Cole, Elmer L.
Sevringhaus

William S. Middleton, Joseph S. Evans, Elmer
L. Sevringhaus

TERRITORY OF HAWAII

Nils P. Larsen, Stewart E. Doolittle, Harry L.
Arnold

DOMINION OF CANADA

Alberta

Maxwell M. Cantor, John W. Scott, George F.
Strong

Manitoba

Fred Cadham, John M. McEachern, George F.
Strong

Fellowship Candidates

Charles Hutchinson A'Court Walton,
Winnipeg (R C A M C)

Sponsors

Fred Cadham, J. Currie McMillan, George F Strong

"RESOLVED, that the following list of 7 be and herewith are elected to Fellowship in the American College of Physicians as of March 31, 1943".

DISTRICT OF COLUMBIA

MEDICAL CORPS, U S ARMY

Hugh Richmond Gilmore, Jr, Fort James C Magee
Sheridan, Ill
Neely Cornelius Mashburn, Ellington James C Magee
Field, Tex

ILLINOIS

Howard Avery Lindberg, Chicago
(M R C, U S A.)

M Herbert Barker, J Roscoe Miller, LeRoy H Sloan

NEW YORK

Roger Sherman Mitchell, Jr, Glens Falls
Robert Collier Page, New York
(M R C, U S A)

Carl R Comstock, William H Ordway, Asa L Lincoln
Willard J Denno, Thomas Klein, Asa L Lincoln

PENNSYLVANIA

Leon Schwartz, Philadelphia
(U S P H S, R)

Harrison F Flippin, William E Robertson, Edward L Bortz

WISCONSIN

George Colville Owen, Oshkosh
(M R C, U S A)

Oscar Lotz, Alfred W Gray, Elmer L Sevringhaus

ELECTIONS TO ASSOCIATESHIP

December 13, 1942

*Associateship Candidates**Sponsors*

ALABAMA

Ivan Columbus Berrey, Birmingham
John Day Peake, Mobile
Justus MacIlwaine Barnes, Montgomery
(M R C, U S A)

Joseph E Hirsh, James S McLester, Fred Wilkerson
Grady O Segrest, Joseph H Little, Fred Wilkerson
J Harold Watkins, James F Alison, Fred Wilkerson

ARIZONA

Kent Hanthorn Thayer, Phoenix
(M R C, U S A)

George F Aycock, Daniel B Faust, James J Waring

CALIFORNIA

Earl Bryning Ray, Belleflower
(M R C, U S A)
Ephraim Philip Engleman, Fresno
(M R C, U S A)
Otto Arndal, Glendale
James Hallam Cope, Jr, Livermore
Lewis Thomas Bullock, Los Angeles
John Langdon Gompertz, Piedmont
(M R C, U S A)
William Dustin Evans, Santa Barbara
(M R C, U S A)

Daniel D Comstock, E Richmond Ware, Roy E Thomas
Stacy R Mettier, H Clare Shepardson, Ernest H Falconer
R Manning Clarke, Eugene L Armstrong, Roy E Thomas
Chesley Bush, Benjamin W Black, Ernest H Falconer
Donald J Frick, Arthur S Granger, Roy E Thomas
Chesley Bush, Benjamin W Black, Ernest H Falconer
William P Corr, Franklin R Nuzum, Roy E Thomas

Association Candidates

Walter Patrick Martin, Santa Barbara
(M R C, U S A)
Lorenz McBurney Waller, Santa Barbara
(M R C, U S A)

Sponsors

William P Corr, Ernest M Hall, Roy E
Thomas
William P Corr, William C Boeck, Roy E
Thomas

COLORADO

Karl Frederick Arndt, Denver
(M R C, U S A)
Frank Bartlett McGlone, Denver
(M R C, U S A)
Arthur C Rest Spivak

Alfred M Wolfe, Edward G Billings, James
J Waring
George F Aycock, Daniel B Faust, James J
Waring
A Lee Briskman, Bernardine T McMahon,
James J Waring

CONNECTICUT

Lawrence Shapiro Ward, New London

Louis H Nahum, Barnett Greenhouse, Charles
H Turkington

DELAWARE

Constance Anthony D'Alonzo, Wilming-
ton (M R C, U S A)

George H Gehrman, John H Foulger, Lewis
B Flinn

DISTRICT OF COLUMBIA

General Profession

Joseph Edward Brackley, Washington
(M R C, U S A)
Ernest Quong King, Washington
(M R C, U S A)
Lawrence Elias Putnam, Washington

Hugh H Hussey, Eugene R Whitmore, Wal-
lace M Yater
Karl W Brimmer, Russell M Wilder, Wallace
M Yater
Theodore G Klumpp, Walter A Bloedorn,
Wallace M Yater

MEDICAL CORPS, U S NAVY

Otto Leo Burton, Silver Spring, Md
George Neely Raines, Bethesda, Md
Fitz-John Weddell, Jr, Washington, D C

John T Bennett, Edward H Cushing, Ross T
McIntire
Robert E Duncan, Arthur M Master, Ross T
McIntire
Clyde W Brunson, Albert G Bower, Ross T
McIntire

U S PUBLIC HEALTH SERVICE

Irving Donald Fagin, Detroit, Mich
Carl Jacob Kornreich, Staten Island,
N Y

Alpheus F Jennings, Samuel S Altshuler,
Patrick L Ledwidge, Thomas Parran
Arthur C DeGraff, Thomas Parran

FLORIDA

Elwyn Evans, Winter Park

Kenneth Phillips, Spencer A Folsom, Turner
Z Cason

GEORGIA

Harry Parks, Atlanta
(M R C, U S A)
Joseph Alvin Leaphart, Jesup
Charles Bennett Fulghum, Sr, Milledge-
ville

Joseph Yampolsky R Hugh Wood, Glenville
Giddings
James C Metts, J Reid Broderick, Glenville
Giddings
Thomas L Ross, Jr, Harold C Atkinson, Glen-
ville Giddings

ILLINOIS

Clarence Edward Merkle, Alton
Arthur Bernstein, Chicago
Herman Felix DeFeo, Chicago
Joseph Charles Ehrlich, Chicago
(M R C, U S A)

Ralph A Kinsella, Joseph F Bredeck, Cecil
M Jack
Sidney A Portis, Aaron Arkin, LeRoy H Sloan
Italo F Volini, Leo L Hardt, LeRoy H Sloan
Robert W Keeton, Italo F Volini, LeRoy H
Sloan

Associateship Candidates

Frederick William Fitz, Chicago
(M R C, U S A)
Carl August Johnson, Chicago

Clayton Jackson Lundy, Chicago
(M R C, U S A)
Hugh Barrett O'Neil, Chicago

Carl Otto Rinder, Chicago

Irving Elihu Steck, Chicago

Solomon Carl Werch, Chicago

Ralph Waldo Trimmer, Oak Park

Howard Dick Countryman, Rockford
(M R C, U S A)
Arvid Theodore Johnson, Rockford

Morris Caplinger Thomas, Indianapolis
(M R C, U S A)

Julian Ewart McFarland, Ames

Edward Sumner Brewster, Boone
(M R C, U S A)
George Elmer Mountain, Des Moines

Earl Save, Topeka
(M R C, U S A)
Frederic Wilhelm Hall, Winfield
(M R C, U S A)

John Samuel LaDue, New Orleans
George Rodney Meneely, New Orleans

Leonard Collier Paggi, New Orleans
Paul Jasper Thomas, New Orleans

Lee Williamson, New Orleans
(M R C, U S A)

David Sydney Sherman, Brookline

Gerald Norman Rein, Benton Harbor
Raymond Kenneth Bartholomew, Detroit

Henry Alexander Bradford, Detroit
(M R C, U S A)
Louis Sanderson Lipschutz, Detroit
(M R C, U S A)
James Murdock MacMillan, Detroit

Sponsors

J Roscoe Miller, Andrew C Ivy, LeRoy H Sloan
Arthur R Elliott, Grant H Laing, LeRoy H Sloan
Lee C Gatewood, Willard O Thompson, LeRoy H Sloan
M Herbert Barker, J Roscoe Miller, LeRoy H Sloan
Arthur R Elliott, Joseph A Capps, LeRoy H Sloan
Robert W Keeton, George E Wakerlin, LeRoy H Sloan
Andrew C Ivy, Alexander A Goldsmith, LeRoy H Sloan
Willard O Thompson, Lee C Gatewood, LeRoy H Sloan
Clarence H Boswell, Harold D Palmer, LeRoy H Sloan
Walter L Palmer, Willard O Thompson, LeRoy H Sloan

INDIANA

Frank L Jennings, Harold C Ochsner, Robert M Moore

IOWA

John H Peck, John C Parsons, Benjamin F Wolverton
Walter L Bierring, John C Parsons, Fred M Smith, Benjamin F Wolverton
Harry L Smith, Philip W Brown, Edgar V Allen, Benjamin F Wolverton

KANSAS

William C Menninger, James G Stewart, Harold H Jones
George A Westfall, Daniel V Conwell, Harold H Jones

LOUISIANA

Robert H Bayley, Louis A Monte, Edgar Hull
Edgar Hull, William S McCann, Joseph E Knighton
Louis A Monte, Robert H Bayley, Edgar Hull
John H Musser, Grace A Goldsmith, Edgar Hull
Edgar Hull, Joseph O Weilbaecher, Jr, Joseph E Knighton

MASSACHUSETTS

James M Faulkner, John A Foley, William B Breed

MICHIGAN

John V Fopeano, John D Littig, Henry R Carstens
Frank J Sladen, Frank R Menagh, Douglas Donald
F Janney Smith, Frank J Sladen, Douglas Donald
Rudolf Leiser, Louis J Bailey, Patrick L Ledwidge
Frank J Sladen, John G Mateer, Patrick L Ledwidge

Associateship Candidates

Louis Adrian Schwartz, Detroit
(M C, U S N R)
Wesley Van Camp, Detroit
(U S P H S, R)
Harris Vincent Lilga, Petoskey

Sponsors

Hugo A Freund, Warren B Cooksey, Patrick
L Ledwidge
Gordon B Myers, Warren B Cooksey, Patrick
L Ledwidge
Floyd H Lashmet, Russell L Haden, Douglas
Donald

MINNESOTA

Royal V Sherman, Red Wing
Lawrence Harvey Beizer, Rochester
(M R C, U S A)
John Daniel Call, Rochester
Thornton Tayloe Perry, III, Rochester
(M R C, U S A)

Jay C Davis, Archibald E Cardle, Edward H
Rynearson
Herbert Z Giffin, Charles H Watkins, Edgar
V Allen
David M Berkman, Arlie R Barnes, Edward
H Rynearson
Nelson W Barker, Edgar A Hines, Jr, Edgar
V Allen

MISSOURI

Joseph Henry Delaney, Columbia
(M R C, U S A)
Louis Aloysius Scarpellino, Kansas City
Edward Massie, St. Louis

Dan G Stine, William B Brown, Ralph Kin-
sella
Peter T Bohan, Paul F Stookey, Ralph Kin-
sella
David M Skilling, Jr, Harry L Alexander,
Ralph Kinsella

NEBRASKA

Charles Edward Thompson, Omaha

Rodney W Bliss, George P Pratt, Warren
Thompson

NEW JERSEY

Levi Moore Walker, Atlantic City
(M R C, U S A)
Samuel Thomas Busansky, Browns Mills
Richard Wagner, Elizabeth
(M R C, U S A)
Cornelius C Perrine, Fair Haven
Alfred Leon Kruger, Jersey City
(M R C, U S A)
Ralph Miller, Newark

Hilton S Read, Samuel L Salasin, George H
Lathrope
Marcus W Newcomb, Martin H Collier,
George H Lathrope
Arturo R Casilli, Harry Bloch, George H
Lathrope
Frank J Altschul, Carlos A Pons, George H
Lathrope
Abraham E Jaffin, Berthold S Pollak, George
H Lathrope
Aaron E Parsonnet, Jerome G Kaufman,
George H Lathrope

NEW YORK

Walter Kent Van Alstyne, Binghamton
Charles John Crawley, Brooklyn
Isidore Albert Feder, Brooklyn
(M R C, U S A)
Victor Grover, Brooklyn
Saul Michalover, Brooklyn
(M R C, U S A)
Israel Abraham Schiller, Brooklyn
(M R C, U S A)
David Hale Clement, Buffalo
Jay Ignatius Evans, Buffalo
Edward Royal Henry Kurz, Glendale
Samuel Hurwitz, Jamestown
(M C, U S N R)

Ralph J McMahon, George C Hamilton, Nel-
son G Russell, Asa L Lincoln
Alexis T Mays, William A Lange, C F Ten-
ney
Maurice J Dattelbaum, Irving J Sands, Asa L
Lincoln
Edwin P Maynard, Jr, William H Lohman,
Asa L Lincoln
Benjamin M Eis, Irving J Sands, Asa L
Lincoln
Irving J Sands, Herbert R Edwards, Asa L
Lincoln
Allen A Jones, Abraham H Aaron, Nelson G
Russell
Allen A Jones, Abraham H Aaron, Nelson G
Russell
John G Senese, William H Lohman, Asa L
Lincoln
Frank P Goodwin, Bruce K Wiseman, Nelson
G Russell

Associateship Candidates

Kurt Joseph Berliner, New York
 Simon Dack, New York
 Harry David Fein, New York
 Selian Hebald, New York
 Scott Johnson, New York
 Leon Lewis, New York
 George Charles Linn, New York
 Samuel Melamed, New York
 Robert Anton Newburger, New York
 (M R C, U S A)
 Albert Christy Santy, New York
 Louis Elliott Siltzbach, New York
 Louis Julius Soffer, New York
 Saul L. Solomon, New York
 (M R C, U S A)
 Morris Feldman Steinberg, New York
 Arthur Mandel Tunick, New York
 (M R C, U S A)
 Roy Elias Kinsey, Peekskill
 (M R C, U S A)
 Maurice Anthony Donovan, Schenectady
 Harry E Reynolds, Schenectady
 John Marcus Rice, Watertown

John Harold Kotte, Cincinnati
 Edward Allen Marshall, Cleveland
 (M R C, U S A)
 Oscar Ferdinand Rosenow, Columbus
 Frank William Anzinger, Springfield
 (M R C, U S A)
 David Lynn Beers, Warren
 Harold Ellsworth Hathhorn, Youngstown
 (M R C, U S A)

Frank Thomas Joyce, Chickasha
 (M R C, U S A)
 Charles Edwards Leonard, Oklahoma City

OKLAHOMA

Frederic William Wilson, Franklin
 Ross Kennedy Childerhose, Harrisburg
 Carl Cooke Hoffman, II, Harrisburg
 (M R C, U S A)
 Robert Alexander Houston, Harrisburg
 Bernard J McCloskey, Johnstown
 Samuel Baer, Philadelphia

Sponsors

Samuel S Paley, Samuel H Averbuck, C F Tenney
 Arthur M Master, Herman Lande, Asa L Lincoln
 Norman Jolliffe, Elaine P Ralli, C F Tenney
 Robert A Cooke, Robert Chobot, Asa L Lincoln
 Walter P Anderton, James Alex Miller, Asa L Lincoln
 Asa L Lincoln, Robert M Lintz, C F Tenney
 Robert F Loeb, Frederick R Bailey, Walter W Palmer, Asa L Lincoln
 David Marine, Bernard S Oppenheimer, Asa L Lincoln
 Bernard S Oppenheimer, Norman Jolliffe, C F Tenney
 Howard F Shattuck, Arthur J Antenucci, Asa L Lincoln
 Max Pinner, David Ulmar, Asa L Lincoln
 Bernard S Oppenheimer, George Baehr, C F Tenney
 Louis F Bishop, Jr, Herman O Mosenthal, C F Tenney
 Bernard S Oppenheimer, Solomon Silver, C F Tenney
 I Ogden Woodruff, Isidore W Held, C F Tenney
 Paul W Clough, Thurman D Kitchen, Asa L Lincoln
 Lester Betts, Isaac Shapiro, C F Tenney
 Lester Betts, Isaac Shapiro, Asa L Lincoln
 William W Hall, Walter F Smith, Nelson G Russell

OHIO

Johnson McGuire, Hubert H Shook, A B Brower
 Joseph C Placak, Milton B Cohen, A B Brower
 Ray W Kissane, Herbert V Weirauk, Louis Mark, A B Brower
 Carl H Reuter, Benedict Olch, A B Brower
 Leo C Bean, Colin R Clark, A B Brower
 Morris Deitchman, William H Bunn, A B Brower

PENNSYLVANIA

Harvey M Watkins, Kelse M Hoffman, R R Snowden
 Constantine P Faller, Frank F D Reckord, Edward L Bortz
 Constantine P Faller, Carl E Ervin, Edward L Bortz
 Carl E Ervin, Constantine P Faller, Edward L Bortz
 Horace B Anderson, Laurie D Sargent, R R Snowden
 Harold L Goldburgh, Joseph C Doane, Edward L Bortz

Associateship Candidates

Augustus Henry Clagett, Jr, Philadelphia
(M R C, U S A)
Joseph Ferguson Hughes, Philadelphia
Edward Bernard LeWinn, Philadelphia
Pascal Francis Lucchesi, Philadelphia
James Edwin Pugh, Philadelphia
Mayer Albert Green, Pittsburgh
Joseph Edward Harenski, Pittsburgh
Andrew James Parker, Pittsburgh

Sponsors

George C Griffith, George Morris Piersol, Edward L Bortz
Edward A Strecker, Lauren H Smith, Edward L Bortz
Mitchell Bernstein, Joseph C Doane, Edward L Bortz
Rufus S Reeves, Stanley P Reimann, Edward L Bortz
George C Griffith, Joseph T Beardwood, Jr, Edward L Bortz
Harry M Margolis, Milton Goldsmith, R R Snowden
Frederick B Utley, C Howard Marcy, R R Snowden
Frederick B Utley, C Howard Marcy, R R Snowden

RHODE ISLAND

Alphonse William Lupoli, Warwick

William S Streker, James Hamilton, Alex M Burgess

TENNESSEE

James Warrie McElroy, Memphis
(M R C, U S A)

Whitman Rowland, William C Colbert, William C Chaney

TEXAS

Carl Norman Giere, El Paso
John Buckley Fershtand, Fort Worth
Lester Conrad Feener, Harlingen
(M R C, U S A)
Charles Dickens Reece, Houston

Orville E Egbert, James J Gorman, M D Levy
Will S Horn, Caleb O Terrell, M D Levy
Sam E Thompson, Joseph Kopecky, M D Levy
Frederick R Lummis, Homer E Prince, M D Levy

UTAH

Theodore Charles Bauerlein, Salt Lake City

G Gill Richards, William C Walker, Louis E Viko

VIRGINIA

Byrd Stuart Leavell, Charlottesville
Hunter McGuire Doles, Norfolk
Robert Case Manchester, Norfolk
(M C, U S N R)
John Phillip Lynch, Richmond
Gilman Rackley Tyler, Richmond
(M R C, U S A)

Eugene M Landis, Henry B Mulholland, Walter B Martin
Frank H Redwood, C Lydon Harrell, J Edwin Wood, Jr
C Lydon Harrell, Alfred B Hodges, Walter B Martin
Wyndham B Blanton, Douglas G Chapman, Walter B Martin
William B Porter, Harry Walker, Walter B Martin

WASHINGTON

Alice Grace Hildebrand, Seattle
Ernest Marvin Tapp, Walla Walla
Joseph Hawkins Low, Yakima
(M R C, U S A.)

Russell M Wilder, Arlie R. Barnes, Edgar V Allen, Edwin G Bannick
Franklin C Cassidy, Edward L Whitney, Edwin G Bannick
Paul J Lewis, Howard L Hull, Charles E Watts

WEST VIRGINIA

George Paul Heffner, Charleston
Walter Louis Schafer, Wheeling
(M C, U S N R)

Martin L Bonar, Henry L Robertson, Albert H Hoge
William M Sheppe, Delivan A MacGregor, Albert H Hoge

*Associateship Candidates**Sponsors*

WISCONSIN

Michael W Shutkin, Milwaukee

Elston L Belknap, Norbert Enzei, Elmer L Sevringhaus

Roger Clifton Cantwell, Shawano

Guy W Carlson, Grant H Laing, Elmer L Sevringhaus

CANAL ZONE

Elmer Roger Smith, Ancon
(M R C, U S A)

Samuel M Browne, Maurice Hardgrove, Gilbert M Stevenson

TERRITORY OF HAWAII

Harry Loren Arnold, Jr, Honolulu

Stewart E Doolittle, Hastings H Walker, Harry L Arnold

DOMINION OF CANADA

Ontario

William Addison Guest, Ottawa

John E Plunkett, Trenholm L Fisher, Warren S Lyman



OBITUARY

ALGERNON BRASHEAR JACKSON

On October 22, 1942, death came suddenly but quietly to Dr Algernon Brashear Jackson, Washington, D C, a former Professor of Bacteriology, Preventive Medicine and Public Health at Howard University The cause of his death was myocarditis due to hypertension

During Dr Jackson's forty-one years of service in the medical profession he found time as a hobby to compose music and write short plays and stories He played well the piano for the enjoyment of his family and friends, his preference was classical music Dr Jackson was primarily a physician with the soul of a poet, with many talents of an accomplished musician and popular author Even though he was the author of more than a score of publications in medical journals, the three books published by him dealt with the less scientific aspects of human life

Algernon Brashear Jackson, the son of Charles A and Sarah L Brashear Jackson, was born May 21, 1878, in Princeton, Indiana His primary, secondary and collegiate education was received in the schools of Indiana, his medical education was obtained at the Jefferson Medical College of Philadelphia, from which he was graduated in 1901 His medical career had several sides, with organization, administration and health education playing major rôles He began the practice of medicine at Philadelphia in 1901 and continued until 1921 During these twenty years he spent thirteen of them as assistant surgeon at the Philadelphia Polyclinic Hospital and the Graduate School of Medicine of the University of Pennsylvania He was one of the founders of the Mercy Hospital of Philadelphia, serving as its Surgeon-in-Chief for fifteen years, and as its Superintendent for nine years During the first world war he was assigned by the Surgeon General's Office to the activities of training camps with responsibilities directed toward the prevention of venereal diseases

In 1920, Dr Jackson married Miss Elizabeth A Newman, R N, the daughter of Mr and Mrs Harden Newman, of Media, Pennsylvania The rest of his life was one of marital happiness and mutual appreciation In 1921, he resigned as Superintendent of the Mercy Hospital of Philadelphia, which had then moved to its present site, to accept an appointment on the faculty of medicine of Howard University He was a member of the staff of Howard University from 1921 to 1934, when he resigned his position as Professor and Administrative Head of the Department of Bacteriology, Preventive Medicine and Public Health, in order to give full-time service to private practice, confining most of this work to the field of his special interest, gastro-enterology He was actively engaged in this type of practice when death came, and was improving his basic technic in this field by returning for refresher courses during summer months to the postgraduate schools of the University of Pennsylvania and Columbia University

Dr Jackson was one of the founders of the Greek letter fraternity, Sigma Pi Phi, known as the "Boule," whose membership was composed of college graduates only. He traveled widely in the United States and was well known for his public health and health education lectures and writings, especially for those phases where the Negro seemed to be involved. At the request of the National Medical Association and the National Hospital Association, he made a 14,000 mile tour of the Negro hospitals in thirteen southern states in 1929, the report of the findings together with his recommendations for corrections of certain defects did much to improve their standards and recognitions.

In his early medical career he did considerable surgery, operating in the hospitals of Philadelphia and for groups at clinics in other parts of the country. In recognition of his work as a physician and surgeon, administrator, original investigator and contributor to medical literature, he was made a Fellow of the American College of Physicians in 1917. This was one of his most cherished recognitions.

His contributions to medical literature were many, special mention may be given to his widely quoted publications on the results of magnesium sulfate injection in the treatment of rheumatism as early as 1911. The lay public read and benefited greatly by his many press releases on health, written in simple terms for their benefit.

Among his memberships in medical organizations we list the following: Fellow of the American College of Physicians, Member, National Medical Association, National Hospital Association, National Tuberculosis Association, American Public Health Association, John A. Andrew Clinical Society and Medico-Chirurgical Society of the District of Columbia.

Dr Jackson was an Episcopalian by faith.

HILDRUS A. POINDEXTER, M.D.,
Dean, Howard University

ANNALS OF INTERNAL MEDICINE

VOLUME 18

FEBRUARY, 1943

NUMBER 2

NEWER KNOWLEDGE OF EPILEPSY *

By WILLIAM G LENNOX, *Boston, Massachusetts*

MORE has been learned about the real nature of epilepsy in the past 20 years than in the preceding 20 centuries. We have only two or three minutes for each year of these 20; therefore, I shall for the most part limit myself to the data which my associates and I have been able to collect.

ECONOMICS OF EPILEPSY

Before considering the science of epilepsy, let us think for a moment of its economics. When our world warring is ended, medicine like every other activity will need to link arms with economics. The amount of money spent in the prevention and treatment of various diseases must be related to the cost of these diseases and to the possibility of restoring their victims to productive activity. Epilepsy is a much larger and more costly problem, and also a more hopeful one, than most persons realize. Epileptics in the United States number something over half a million, as many as the victims of active tuberculosis, of diabetes or of infantile paralysis. The tenth part of these patients who are hospitalized at public expense occupy one-tenth as many hospital beds as all medical, surgical, and obstetrical patients combined. Epileptics, no matter how able-bodied or clear-minded, are denied service in our armed forces and in our industries. As soldiers are killed or brain wounded, both the relative and the absolute numbers of persons subject to convulsions will increase. Attempting to find the cause and cure of seizures is a handful of clinicians and research workers—members of the American Branch of the International League against Epilepsy. Helping to lighten public ignorance and prejudice are such organizations as the Harvard Epilepsy Commission and the Laymen's League against Epilepsy.¹ Their resources are grotesquely small. For purposes of medical research designed to meet the aggressions of epilepsy, this nation in the last two decades has probably not expended the price of a single bomber. Whether the meager thousands were profitably spent you should decide after hearing the résumé which follows.

* Read at the St. Paul meeting of the American College of Physicians May 4, 1942

FASTING AND ITS SEQUELAE

Many a discovery has had a bizarre beginning. Twenty years ago an osteopathic practitioner announced that prolonged starvation had a restraining effect on convulsions. This statement was confirmed by Geyelin,² Talbot,³ and others. The suggestion was early made that this auto-cannibalistic diet might be replaced by one which simulated starvation, a diet containing a plethora of fat and a minimal amount of carbohydrate and protein. This ketogenic diet proved as effective as fasting and far more practical. It is valuable in the treatment of children, especially those having frequent petit mal. Early investigators assumed that the diet was beneficial because of the sedative action of the ketone bodies. However, acidosis induced by other means, such as the administration of large quantities of hydrochloric acid or of acid forming salts, was found to inhibit seizures. For short periods petit mal seizures could be controlled by the inhalation of air rich in carbon dioxide or by the auto-manufacture of lactic acid by means of muscular exercise. Conversely, alkalosis induced by overventilation or by ingestion of large quantities of alkali tended to precipitate seizures. Like a touchdown made from the opening kickoff, it seemed as though these observations had won the game. Epilepsy is an alkalosis; acidify and all will be well. This hope, however, was quickly dissipated. Study demonstrated no abnormality in the acid-base balance of epileptics, but only that an acute upset of the patient's balance would alter the frequency of his attacks. Alkalosis precipitated seizures only in the epileptic. Furthermore, petit mal seizures were more easily influenced by chemical changes than grand mal, a circumstance which seemed to depend, as later study showed, on the peculiar electrical cortical activity associated with petit mal.

Continued investigation disclosed also, that disturbance of the acid-base balance is only one of various factors which may alter the frequency of seizures. In patients subject to petit mal these seizures could be induced by mild degrees of anoxemia and could be inhibited by increasing the oxygen tension in the patient's tissues. The latter condition was accomplished by having patients breathe pure oxygen while in a compression chamber under three atmospheres of pressure.⁴ Temple Fay⁵ helped his patients by dehydrating them, and McQuarrie⁶ induced seizures by a large fluid intake combined with injection of pitiessin. It was found that frequency of seizures could be altered also by changes in the concentration of blood sugar, blood calcium, and possibly also cholesterol and vitamins. Sudden and widespread anemia of the brain should be an effective precipitant of seizures, if old theories of vascular spasm are correct. However, when syncope was induced in 20 patients subject to grand mal, a convulsion was observed in only one. Of more importance, the volume of blood passing through the brain was not decreased immediately before the occurrence of spontaneous seizures.⁷

In this period of search, eager investigators hoped that anoxemia, anemia, hydration, or hypoglycemia was the fundamental cause of epilepsy. Like alkalosis, however, these various conditions were not primary causes but only precipitating factors. They were not the inner mechanism of seizures but the threshold. In the analogy of the overflowing reservoir, they were not the impounded waters, but the restraining dam. Statements should not be too categorical. The secret of epilepsy lies in the chemistry of the discharging neurones of the brain. The relationship of neuronal and of bodily chemistry has yet to be clarified. The amazingly low oxygen tension of the brain recently announced by Bronk⁸ is illustrative. Another example is the action of anti-convulsant drugs. Bromides and phenobarbital are sedatives, whose soothing influence is useful in many conditions, and apparently of value in epilepsy only because they increase the seizure threshold. On the other hand, the drug whose worth was proved by our colleagues Merritt and Putnam⁹ has little hypnotic effect, seems to have value only in epilepsy, and in some instances at least not only stops seizures, but composes the underlying disordered electrical potentials of the brain. I refer to sodium diphenyl hydantoinate (dilantin sodium, or, officially, phenytoin sodium), the drug of choice in epilepsy. That this drug is relatively ineffective for petit mal, a type of seizure so readily affected by changes in pH, in carbon dioxide tension, and in the glucose content of the blood, points the need and the opportunity for further research.

Having uncovered the valuable facts which have been mentioned, laboratory workers were at a loss for an approach to the core of the problem, the cause or causes of seizures. Beginning with Hippocrates, clinicians have advanced many different groups of causes. At present, four principal ones are recognized. In inverse order of importance, these are emotional, somatic, pathologic brain lesions, and heredity. For the purpose of ascertaining the importance of these factors, records were analyzed of some 2,000 patients examined by cooperating neurologists throughout the country. Of these clinic and private patients, approximately three-fourths gave no history or, on examination, no evidence of brain injury or of a physical or emotional disturbance which could be considered the primary cause of seizures. In the remaining 25 per cent of patients, the cause in practically all was assigned to some lesion of the brain.

Is the preponderant "unknown" area of epilepsy synonymous with heredity? Are lesions of the brain alone sufficient to explain seizures? These questions bring us to the old contested area of "essential" versus "symptomatic," which overlies the still more ancient battleground of "heredity" versus "environment." Hippocrates placed himself on the side of heredity. Through the centuries words have been hurled back and forth with vigor but only rarely have they been edged with facts. The electroencephalograph is a new and potent weapon, a rifle come to the aid of bows and arrows.

ELECTRICAL PULSATIONS OF THE BRAIN

A few years ago research in epilepsy had reached a blind alley. The secrets of the human brain, hidden behind the bony wall of the skull, seemed inscrutable. Then two discoveries breached this wall. First Myerson, Halloran and Hirsch,¹⁰ psychiatrists of Boston, found that a needle could safely be inserted into the lumen of an internal jugular vein. Blood withdrawn in this manner provided a means of studying the metabolism of a patient's brain. Second, Berger,¹¹ a psychiatrist in Germany, demonstrated the feasibility of recording electrical pulsations of the cortex which were transmitted through the skull. Research of the last few years has been based on these two technics.

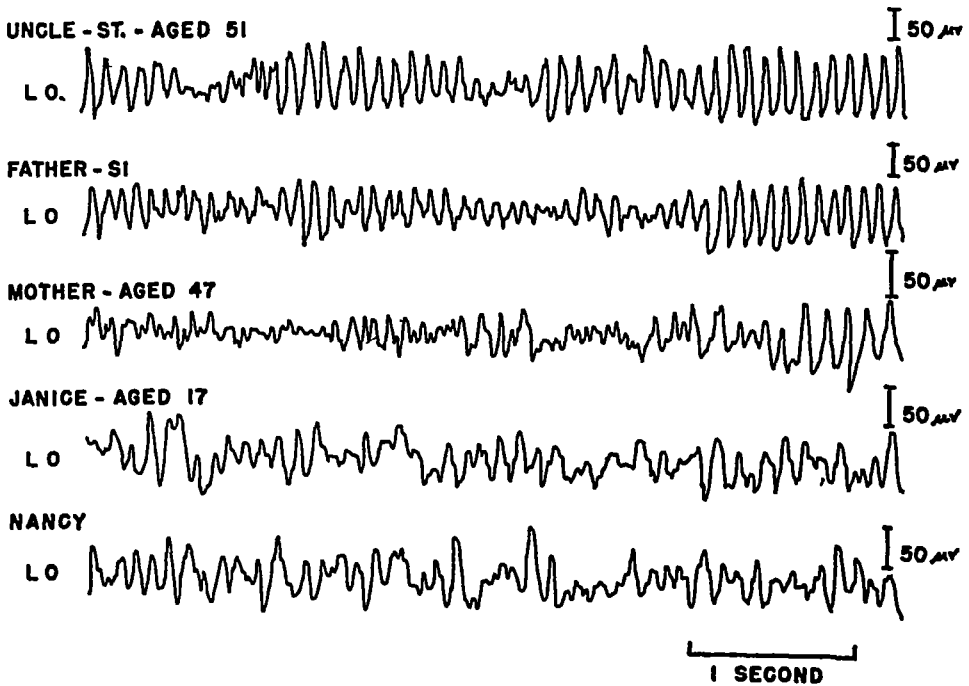


FIG 1 The electrocardiographic records of identical twins, aged 51, the wife of one, and the twin daughters of this union. All are without personal or family history of seizures, yet the records of the mother and the twin daughters are irregular in frequency and voltage. The signal at the right of each tracing indicates microvolts, and the horizontal line at the bottom marks one second.

The subject of electroencephalography as it applies to the problem of epilepsy can be dealt with only in headline fashion. Pronounced disturbances in the pulsations of the electrical waves of the brain are present in all patients during epileptic seizures and in about 90 per cent of patients in a seizure-free period. The three main types of seizures are characterized by different types of dysrhythmia. Interparoxysmal seizure discharges, although usually widely dispersed over the cortex, may in certain patients be confined to a certain discharging area. Epilepsy may be called a cerebral dysrhythmia. The adjective "a" requires emphasis because disordered patterns of brain waves are not confined to persons who are subject to seizures, but are present

in an undue proportion of individuals whose conduct or whose psychical processes are abnormal behavior problem children, "psychopathic personality" adults, alcoholics, and inmates of prisons. Dysrhythmia is also present in a small proportion of persons who by all ordinary standards are normal.¹²

Thus electroencephalography has proved of the greatest use in the understanding and the diagnosis of epilepsy, in the localization of cortical lesions, and to a smaller extent in judging the success of treatment. Recently an even wider field of potential usefulness has appeared. In spite of the fluid-like characteristics of brain waves and their alterability by changes in brain activity or brain chemistry, the pattern of the waves under standard conditions has individuality. In fact, this pattern seems to be a hereditary trait. The evidence for this bold statement lies in a study of the brain waves of twins. In the early days of this technic Davis and Davis¹³ examined nine identical twins and found that the wave patterns of twins were alike. Recently Dr. and Mrs. Gibbs and I have made records of 77 twins, similar or dissimilar, normal or epileptic. In general the brain waves of similar twins who have not suffered brain injury are indistinguishable, whereas the waves of dissimilar twins are unlike. This statement is based on a study of 56 twins (44 monozygotic and 12 dizygotic) who were not subject to seizures or had not suffered brain injury. The "normal" monozygotic twins included 15 whose records were classed as abnormal. Mrs. Gibbs, who interpreted the records, was asked to decide which records were or were not identical. In 86 per cent of the cases her judgment coincided with the clinical evidence of identity, in 11 per cent she was doubtful, and in 5 per cent she was wrong. This 86 per cent represents a high correlation for such a fluid trait. The brain waves of twins of two generations are shown in the accompanying figure. The twin girls have similar but abnormal brain waves. The record of the mother is also abnormal, whereas those of the father and his twin brother are similar and normal. The dysrhythmia of the daughters, therefore, came from the mother.

If the brain wave pattern is an hereditary trait, it should be possible to trace the heredity of conditions which are associated with disordered brain rhythms, and to determine persons who are "carriers" of the disorder, and incidentally to settle the old question of heredity versus environment in the etiology of epilepsy. With this end in mind, electroencephalographic tracings have been made of 312 members of the epileptics' immediate family. Fifty-two per cent of these tracings were classed as definitely abnormal, 11 per cent as doubtful, and 37 per cent as normal. Thus the incidence of dysrhythmia either in the general population or among the patient's near relatives is at least 20 times the incidence of epilepsy in the general population or among the relatives of patients. Even more significant from the standpoint of genetics are the results obtained when both parents of patients were tested. This has been done for 88 families. In 27 per cent both parents had definite dysrhythmia, which is 27 times the expected number if one person in 10 is

dysrhythmic In only 9 per cent of the families were the records of both parents clearly normal

Returning to the subject of twins, study was made of 19 twins, in whom one or both members were subject to seizures Of this group, there were six identical twins, neither of whom had a history suggestive of brain injury and both of whom had dysrhythmia In three cases both of the twin members had seizures, and in three cases the unaffected member has had a seizure after the original electrical records were made There were also six identical twins of whom only one co-twin had had a seizure Because the co-twins have the same heredity, either heredity is of no account in the affected twin, or his seizures must be due entirely to environmental causes This is the alternative usually discussed, but the electrical studies indicate that neither is correct In five of these identical twins, only one of whom has chronic epilepsy, the normal co-twin's electrical record was, like the patient's, abnormal In each instance the patient had suffered brain injury The sixth twin furnished an example of what might be called temporary symptomatic epilepsy One of identical twin girls had a few convulsions and dysrhythmia following a cerebral concussion Several months later seizures had not recurred, and brain waves had become normal and indistinguishable from those of her twin sister

These electrical studies lead to the conclusion that manifest epilepsy is not inherited but that a predisposition or susceptibility is inherited A similar statement might be made about diabetes, obesity, hypertension and many other disorders The unique feature about epilepsy is the suggestion that the predisposition may in most instances be disclosed by electrical tracings, and these laboratory recordings may be of great value to the physician, to the patient and to society when decision must be made with reference to marriage and procreation

The facts here presented must be viewed against the background of other facts, namely that except for the three a second alternate dart and dome formation of petit mal, the dysrhythmia of epilepsy is not peculiar to it Dysrhythmia may accompany paroxysmal disorders of conduct, or of thought, or for all we know, may accompany genius or high achievement Eugenics, prolific in promises, has proved sterile in practice because eugenic measures, to be effective in a reasonable number of centuries, must be applied not only to the victims of a disorder but to the much larger numbers of healthy "carriers" If persons with pronounced dysrhythmia are the healthy "carriers" of epilepsy and allied disorders, including, perhaps, genius, then electroencephalography is a technic capable of improving the race and undoing some of the eugenic ravages of war

CHEMICAL ETIOLOGY OF EPILEPSY

Persistent search for the answer to certain problems results in discovery of the answers, but often these answers lead only to problems far more dif-

ficult Puzzles which intrigued the investigators of epilepsy several decades ago—allergy, gastrointestinal functions, metabolism of the body as determined by analysis of the urine, spinal fluid, or of blood drawn from an arm vein—have been answered in the negative and now seem naive and futile. Search for the answer to epilepsy has led to the brain, and past all dead or foreign tissues of the brain to its functioning, discharging cells. Investigators must now accomplish the impossible and peer within these and other cells.

Behind the neurones of the brain lie the germinal tissues. Germ cells, we are told, are packed with genes, each gene presumably a large protein molecule. The particular germ cell which is antecedent to the epileptic contains a gene or genes which when transferred to the neurones of the brain give these cells a peculiar chemical composition or reaction, which in turn disturbs their normal rhythmic discharge. The same germ cell may or may not contain another gene which results in disturbance of the normal rhythm of the autonomic nervous system (migraine) or a gene which represents mental deterioration, or a gene which produces various physical dyssymmetries.

The disturbances in the pulsations of discharging clusters of neurones can be registered by the electroencephalograph. The chances are many to one that these peculiar pulsations will not be accompanied by any unusual behavior of the individual. He has asymptomatic dysrhythmia, a condition which was unknown and unsuspected until the recent arrival of prying medical scientists. In a minority of dysrhythmic individuals, however, because of injury or other environmental influences, the unusual electrical pulsations become externalized and accompany unusual patterns of thought or of physical behavior. When paroxysmal, these unusual actions have been called grand mal, petit mal, or psychic seizures. Doubtless there are other conditions not ordinarily called epilepsy, characterized by periods of unsocial behavior, which physiologically are allied to epilepsy and should be treated as problems for the doctor and the chemist and not primarily problems for the preacher or the prison.

There is another type of epilepsy which is not based on a constitutional defect of discharging cells, but arises through the injury or the disturbance of cells which were normal. Such injuries whether mechanical or chemical may give rise to dysrhythmia, which may be short-lived and asymptomatic, or may gradually increase and spread until seizures result. This is the condition, probably rare, of symptomatic epilepsy.

Dramatic are the advances achieved through use of Berger's discovery, but behind the peculiar electrical pulsations of the brain lies the unknown chemistry of discharging nerve cells. At this point a study of the blood as it passes through the brains of patients, and as it influences the electrical pulsations of the brain, is crucial. Studies made possible by the technic of Myerson, Halloran and Hirsch¹⁰ have shown that in normal subjects the respiratory quotient of the brain is unity and the metabolism of the brain is closely dependent on that of glucose. The arterial and internal jugular

blood contains a lower concentration of carbon dioxide in petit mal patients than in normal persons. Also in these patients the respiratory quotient of the brain is below unity and the brain burns less glucose per unit of oxygen than it should.

These chemical-electrical studies have demonstrated the relatively large importance of carbon dioxide in the activity of the brain. Small changes in carbon dioxide tension are of far greater importance than small changes in the tension of oxygen. In states of anoxemia sufficient to produce unconsciousness and dysrhythmia the addition of carbon dioxide will restore consciousness and a normal rhythm. In addition to increasing the oxygen saturation of arterial blood, and its oxygen dissociation curve, carbon dioxide has a specific effect in altering the cerebral circulation so that fluctuations in the carbon dioxide tension of the brain are minimized. Studies of brain metabolism in relation to the successful treatment of dysrhythmia in the individual seem not incapable of solution. Great is the gain scored by phenytoin sodium. There is no reason why other, and even more effective, drugs should not be found.

The term heredity has a fatalistic connotation. Two facts mitigate hereditary influence in relation to epilepsy. First, the indicator of heredity, dysrhythmia, is not in itself enough to produce epilepsy. Some insult to the brain in the form of physical injury or physiological upset is also required and may possibly be avoided. Second, dysrhythmia itself is a fluid characteristic and may possibly be modified by chemical means.

Truly gains against epilepsy in the past 20 years have been great, but more conclusive action is possible, if funds and gifted searchers address themselves to the task. This task is 20 times greater, 20 times more important than the control of seizures. Physician scientists must learn to control the disturbed brain waves of persons who carry a predisposition to epilepsy or to some disorder physiologically allied to it.

REFERENCES

- 1 LENNOX, W. G. Science and seizures, 1941, Harper & Brothers, New York
- 2 GEYELIN, H. R. Relation between the acid and alkali of the blood in epilepsy, Jr Am Med Assoc, 1923, lxxxix, 330
- 3 TALBOT, F. Treatment of epilepsy, 1930, Macmillan, New York
- 4 LENNOX, W. G., and BEHNKE, A. R. Effect of increased oxygen pressure on the seizures of epilepsy, Arch Neurol and Psychiat., 1936, xxxv, 782
- 5 FAY, TEMPLE. The therapeutic effect of dehydration on epileptic patients, Arch Neurol and Psychiat., 1930, xxiii, 920
- 6 McQUARRIE, I., and PEELER, D. B. The effects of sustained pituitary antidiuresis and forced water drinking in epileptic children, Jr Clin Invest, 1931, x, 915
- 7 GIBBS, F. A., LENNOX, W. G., and GIBBS, E. L. Cerebral blood flow preceding and accompanying epileptic seizures in man, Arch Neurol and Psychiat., 1934, xxxii, 257
- 8 BRONK, D. W., and BRINK, F. Energy requirements for the maintenance of structure and function in nerve. Paper read before the American Physiological Society, Boston, April, 1942

- 9 MERRITT, H H, and PUTNAM, T J Sodium diphenyl-hydantoinate (dilantin sodium) in the treatment of convulsive disorders, Jr Am. Med Assoc., 1938, cxi, 1068
- 10 MYERSON, A, HALLORAN, R D, and HIRSCH, H L Technic for obtaining blood from the internal jugular vein and internal carotid artery, Arch Neurol and Psychiat., 1927, xvii, 807
- 11 BERGER, H . Ueber das Elektrenkephalogramm des Menschen, Arch f Psychiat, 1929, lxxxvii, 529
- 12 GIBBS, F A, and GIBBS, E L Atlas of electroencephalography, 1941, Cummings, Cambridge.
- 13 DAVIS, H, and DAVIS, P A Action potentials of the brain in normal persons and in normal states of cerebral activity, Arch Neurol and Psychiat, 1936, xxxvi, 1214

THE FRAUDULENT USE OF DIGITALIS TO SIMULATE HEART DISEASE *

By O F HEDLEY, M D , F A C P , Surgeon, U S Public Health Service,†
Bethesda, Maryland

DURING the summer of 1937, nationwide attention was attracted by reports in professional publications and in the lay press of an extensive criminal racket based on attempts to obtain payments on disability insurance by feigning heart disease. The writer was detailed as medical advisor to the U S District Attorney in New York City, and in that capacity obtained information upon which this report is based ¹

The malefactions here described came under the jurisdiction of the Federal Government because they involved the use of the United States mail to defraud. Official inquiries were first conducted by postal inspectors. When sufficient evidence was obtained, the investigation was conducted by the U S District Attorney. A number of persons were arrested, arraigned, tried, and convicted. Others were questioned. Where it was evident that State laws had been violated, many of the defendants were subsequently tried before State courts.

METHOD OF OPERATING

This scheme for acquiring money through deceit had its inception during the economic depression, about 1931. Although conducted in the main by two firms of lawyers, it involved physicians, "runners," policyholders, and even employees of life insurance companies. Many innocent persons, especially physicians, were embarrassed and even subjected to grand jury investigations.

During the period before the depression life insurance companies ventured into the field of health insurance to the extent of making available at reasonable rates insurance against total and permanent disability. The amount of insurance obtainable was dependent on the size of the policy. Most companies provided 10 dollars per month coverage for each thousand dollars of life insurance.

The conspirators operated by inducing policyholders of life insurance with total and permanent disability features to make fraudulent claims for disability payment. Policyholders were first approached by lawyers' "runners," or agents who persuaded them to take advantage of the disability clauses in their insurance policies by claiming disability. Often these "runners" were apprised that the policyholders, who were for the most part small business men, were in financial difficulties because of the depression. The "runners"

* Read at the St Paul Meeting of the American College of Physicians April 21, 1942
Received for publication May 4, 1942

† Division of Industrial Hygiene, National Institute of Health

then introduced them to the lawyers who agreed to take their cases on a percentage basis

Inquiries were then made concerning disabilities. In most instances the claimant did not have a sufficient disability to cause him to be totally and, presumably, permanently disabled. In that event it would be necessary to invent a spurious disabling disease or to exaggerate a nondisabling condition. Other claimants were the kind of psychoneurotic individuals who resort to litigation on the slightest pretense. In addition, unfortunate persons with conditions sufficient to justify claims for disability fell into the hands of these conspirators, and were put to the expense of paying exorbitant fees which could have been avoided. Sometimes they were induced to withhold claims for disability until they obtained additional insurance through misrepresentation. The lawyers even went so far as to pay the premiums.

Heart disease was frequently used as a claim for disability insurance because it is easy to simulate and difficult to disprove, and because jurors are likely to give the claimant the benefit of any reasonable doubt. After the policyholder had become a client, the next step was to "build up" a clinical picture of heart disease, especially coronary arteriosclerosis with angina pectoris, frequently associated with a spurious attack of coronary occlusion.

The claimant was first coached in the symptoms of coronary insufficiency. In this, the services of physicians were employed, although later the lawyers, with the help of medical textbooks, acquired a working knowledge of these conditions which enabled them to do their own tutoring. The claimant was next induced to visit his family physician with complaints indicating coronary arteriosclerotic heart disease. In most instances the family physician was innocent of unprofessional conduct. The claimant would often give a history suggesting a previous coronary occlusion, taking care that this episode was alleged to occur while away on vacation or under other circumstances in which it was impossible for the family physician to be present.

The next step was to develop evidence which could be used in court. The claimant not infrequently visited several general practitioners. Sometimes he feigned heart disease in a public place, and was often rushed to a hospital. Sometimes he went to a hospital for the treatment of bona fide conditions, and even underwent operations. Here, notations concerning heart disease were made on the records, consultations held, and attacks feigned.

As a final measure to convince the life insurance company or to assure success in event of litigation, an effort would be made to obtain from a reputable cardiologist a consultation report favorable to the claim. The claimant would be sent to the cardiologist by his family physician or by a physician working with the conspirators. The claimant would be coached in the symptoms of heart disease. Frequently, digitalis or some of its derivatives would be administered either to produce an arrhythmia or to produce effects on the electrocardiogram simulating coronary disease. Claimants were often directed to run to the office of the consultant, climb stairs,

drink several cups of coffee, or even go on a debauch. Most of the cardiologists were only guilty of credulity, a shortcoming characteristic of the homo Americana. If his report was favorable, it was subsequently utilized, otherwise, it was consigned to the waste paper basket and another consultation obtained. It is interesting to note that consultations were postponed in order to give the digitalis time to take effect.

Meanwhile, the claimants were instructed to avoid business and remain at home. When sufficient "evidence" had been accumulated, the claims were submitted to the insurance companies for payment of total and permanent disability. On physical examination by physicians of the insurance companies or by qualified consultants, few objective clinical manifestations of organic heart disease would be uncovered. Despite this, the claims were paid at first without much protest because of the well-narrated history and the impressive array of medical testimony. It is extremely difficult to refute a plausible story of heart disease in a middle-aged person, especially in the presence of elevated blood pressure, other signs of arteriosclerosis, diabetes mellitus, or other degenerative diseases. The tendency is to give the claimant the benefit of any reasonable doubt, knowing that juries generally take a similar view.

After a while the conspirators became less careful in the selection of clients. Persons not only in the fifties but also in the forties and even thirties were making claims for disability from heart disease. Although coronary occlusion is by no means rare in persons under age 40, the occurrence of a great number of cases naturally excites suspicion. Well-satisfied claimants not infrequently became "runners" for the lawyers, obtaining fresh business on a percentage basis. The "runners" for the two firms conducted a trade war, each offering better services at cheaper rates, thus disproving the adage that there is honor among thieves. Also, some claimants attempted to pyramid their gains by obtaining insurance from other companies under assumed names.

The claims were invariably handled by the attorneys on a percentage basis. Because of the danger that the claimant might become dissatisfied, talk too much, indulge in physical exercise, return to work, or the depression might end, the attorneys would endeavor to make a cash settlement. This was advantageous to the insurance company which could not foresee how long it would have to continue payments. To the claimant it was frequently disastrous, as he would surrender his life insurance as well as his disability insurance for a relatively small amount, much of which would be used to defray legal expenses.

In a typical case, a person with \$25,000 life insurance with a disability clause providing for the payment of \$250 a month for total and permanent disability would submit a claim for alleged coronary occlusion. It would take about six months to begin payments. The claimant would then receive a check for \$1,500, most of which would go to the lawyers for services rendered. He would then begin receiving \$250 a month, of which about a

fourth went to the lawyers. A cash settlement would then be made for perhaps \$6,000. The lawyers would get \$2,000 of this, and the claimant would surrender his entire life insurance policy for \$4,000.

EXTENT OF CONSPIRACIES

Altogether, 84 persons were actively involved. Of these, six were convicted after trial, 38 pleaded guilty, 16 were indicted but pleaded not guilty, 20 confessed but were not indicted, and two were arrested but not indicted. In addition, there were 155 others against whom there was evidence of guilt but who have not been arrested, or indicted, or have not confessed.

Two physicians were convicted after trial, seven pleaded guilty and were sentenced, three were indicted but pleaded not guilty, 10 confessed but were not indicted, while among 11 others there was evidence of guilt at hand but they were not arrested, indicted, or convicted. Many other physicians unwittingly certified claimants as having heart disease, and were occasioned embarrassment and loss of time.

Life insurance policies amounting to more than 10 million dollars in more than 40 different life insurance companies were involved. Actual payments and cash settlements amounting to several hundred thousand dollars were made. The most important feature of this conspiracy was that as a result of this and other fraudulent practices, the cost of disability insurance has greatly increased, and most insurance companies have ceased issuing this form of insurance. This vitally affects many honest citizens who might otherwise receive this protection.

USE OF DIGITALIS

Digitalis was administered in many cases to produce abnormal electrocardiograms which could be interpreted as due to coronary arteriosclerosis. Although the amount of digitalis given could not be determined with any great degree of accuracy, it appeared that in most cases it was given in comparatively small doses of about 0.1 gram three times a day. In most instances only a flattening of the ST intervals was produced, in others, varying degrees of auriculoventricular block occurred. Premature contractions were infrequently encountered. In the cases in which there were quite marked effects, either the dosage was larger than alleged or individual susceptibility occurred. The most frequent effect of digitalis on the electrocardiogram was to produce a pulling down of the ST segment rather than an actual inversion of a T-wave. In some instances the deeply depressed ST segment simulated a T-wave inversion. In a few instances actual T-wave inversions occurred.

CASE REPORTS

Case 1 White male, aged 45 years, alleged heart attacks simulating coronary occlusion on October 14 and 25, 1933. He subsequently claimed angina of effort, and symptoms of congestive failure such as dyspnea even at rest, severe orthopnea, and

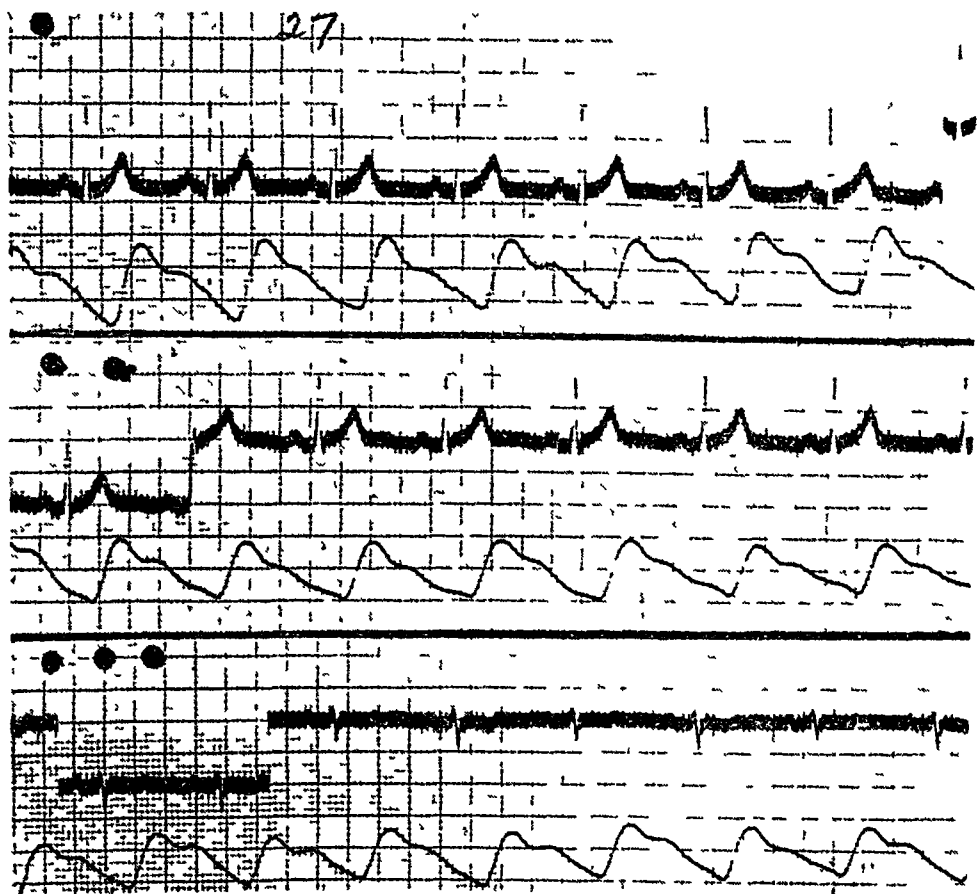


FIG 1 Case 1 Normal electrocardiogram taken by physician representing an insurance company

edema of the lower extremities Other symptoms included Dietl's crisis and intermittent claudication Figure 1 is a normal electrocardiogram taken on March 20, 1934, by a physician representing an insurance company Figure 2 is an electrocardiogram obtained in a hospital on May 26, 1934, after digitalis was administered It shows a true inversion of the T-wave in Lead III, notching and slurring of the QRS

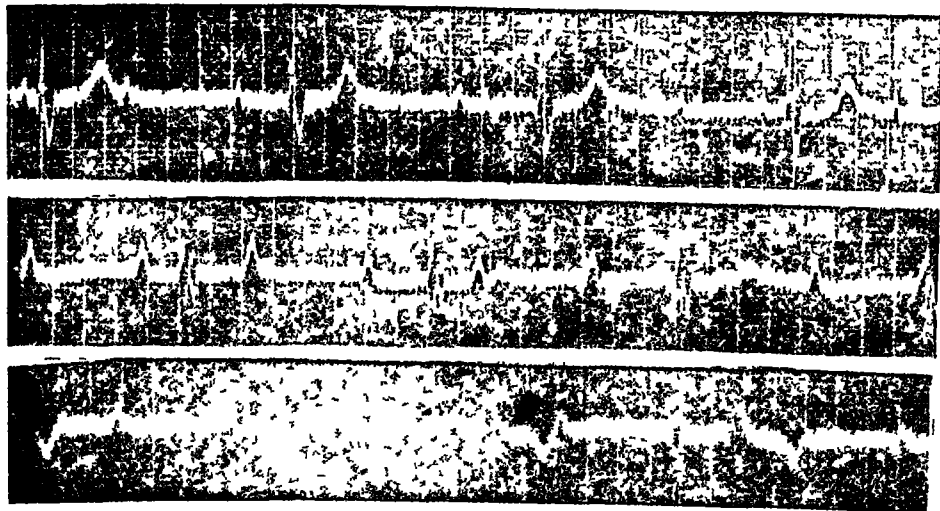


FIG 2 Case 1 Taken in a hospital after digitalis was administered

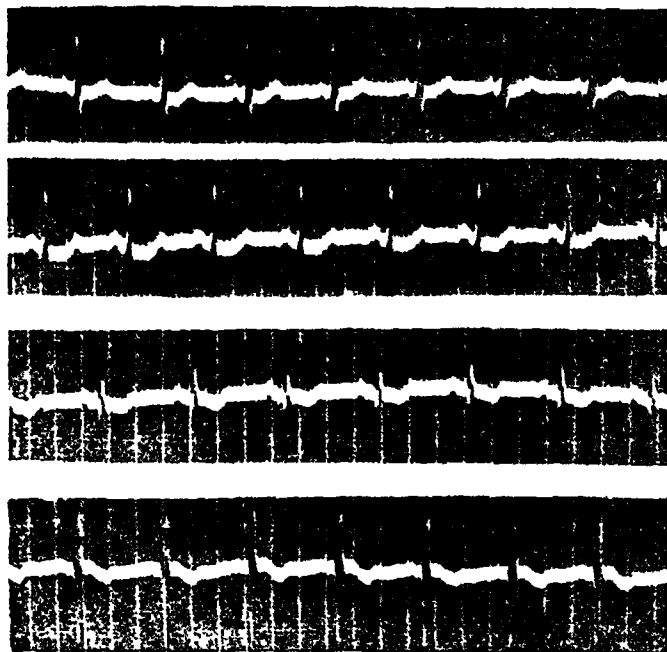


FIG 3 Case 2 Taken after discharge from hospital but postdated to appear as though taken in hospital—shows digitalis effect

complexes in all three leads and complete auriculoventricular dissociation. During a subsequent hospital admission, digitalis was administered surreptitiously with much less effect. Another tracing showed depression of the ST interval in Leads II and III, bradycardia, and inversion of Lead III.

He was admitted to hospitals on four occasions, three of which were spurious admissions to build up the case. The other admission was for appendicitis. On this

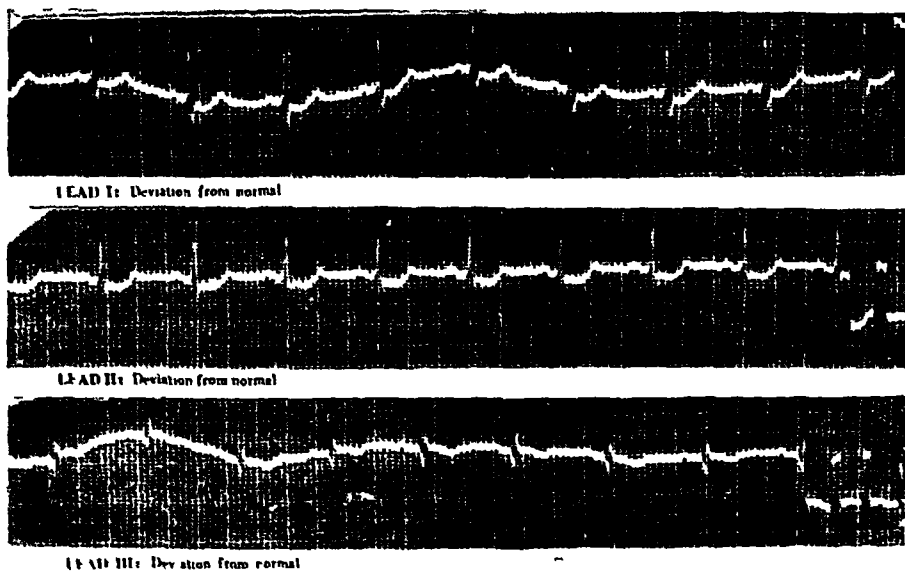


FIG 4 Case 2 Considered indicative of myocardial damage "since digitalis administration has been denied"

occasion the claimant nearly lost his life on the operating table as a result of having one of the physicians in the ring perform the operation. Nevertheless, reference to previous attacks of angina pectoris was added to the records. This claimant also became a "runner" or agent for the attorneys. He subsequently confessed, turned government's evidence, and might have escaped with a suspended sentence had he not literally battered his way into jail for obstructing justice by furnishing information to the defense.

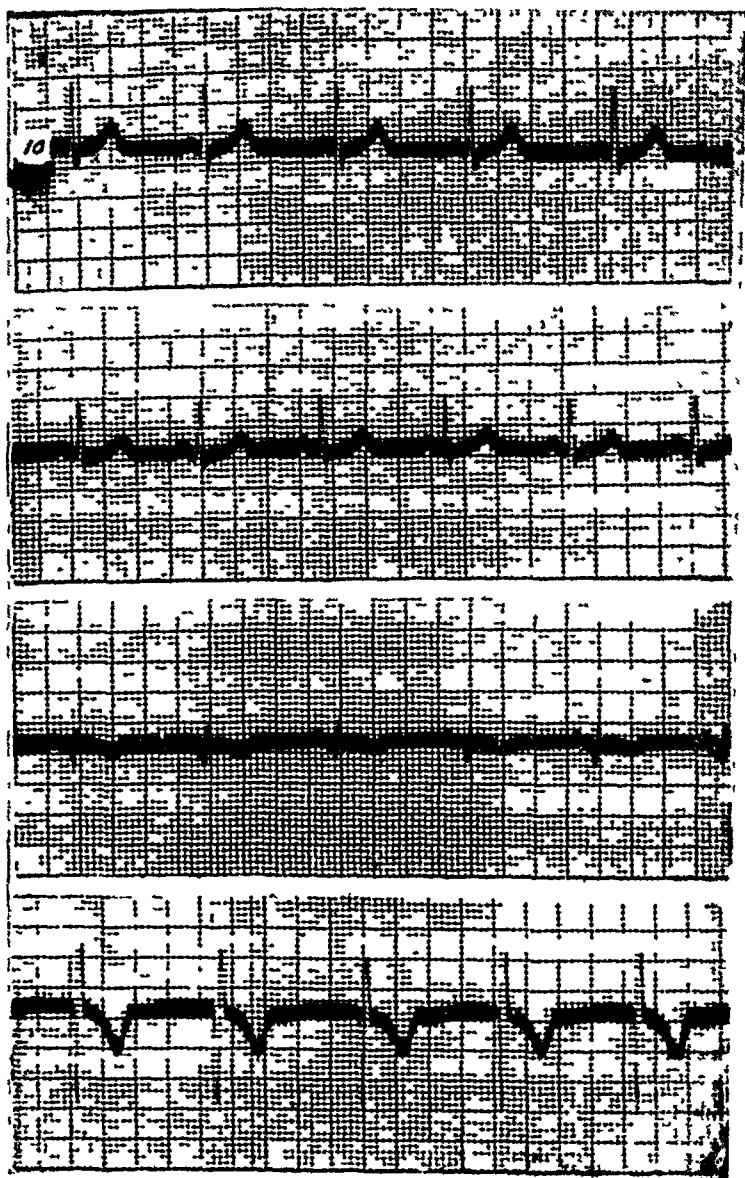


FIG 5 Case 2 Normal electrocardiogram obtained after confession

Case 2 White male, aged 38, claimed angina pectoris and progressive dyspnea beginning in October 1934. In December, he was admitted to a hospital by physicians who were subsequently convicted of participating in this fraud. A tracing, which was taken during this admission, showed depressed ST intervals in Leads I and II, and probably in Lead III, with a diphasic T-wave in Lead III. These findings were regarded as indicative of myocardial damage. He was readmitted to the same hospital by these physicians in July 1935, for a minor automobile accident. No electro-

cardiograms were obtained during this admission. A month later, however, tracings were obtained and postdated to make it appear that they were taken when the claimant was in the hospital. This was proved in court, proof being based on similar tracings seized in one of the defending physicians' offices. This electrocardiogram (figure 3) was interpreted as indicative of myocardial damage. Another tracing, which was taken at the office of a life insurance company, also shows depression of the ST

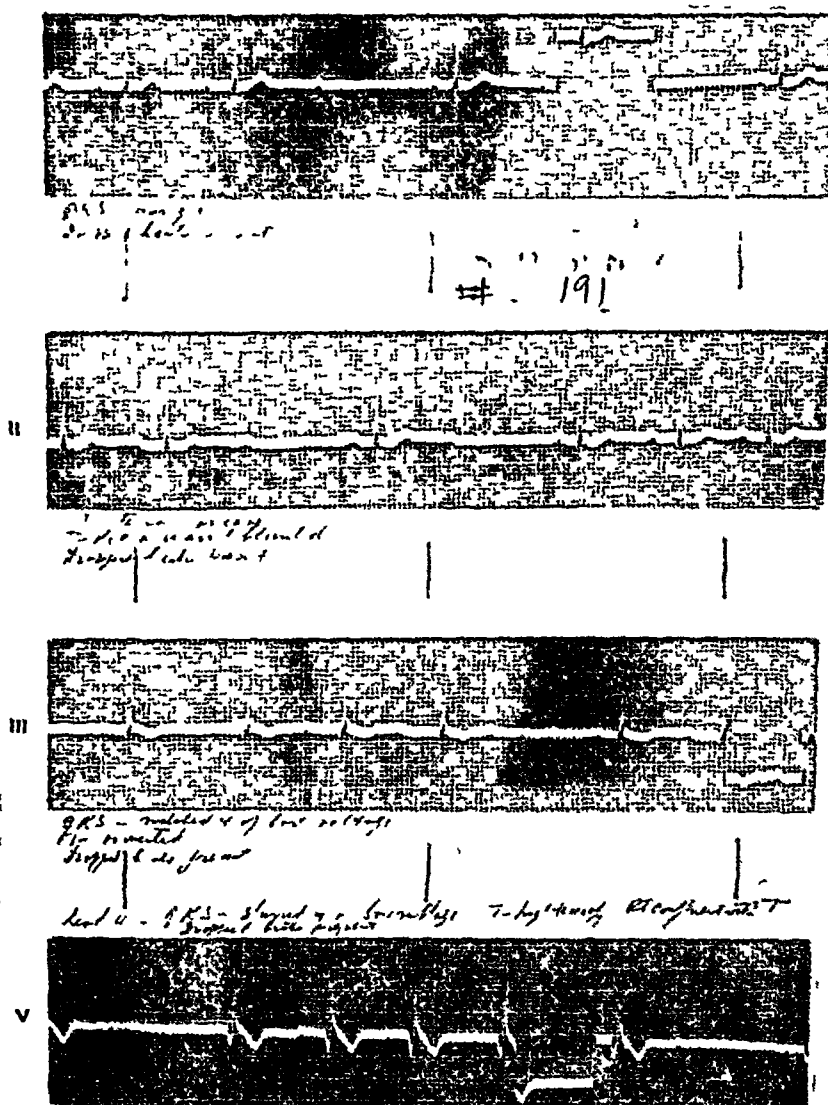


FIG 6 Case 3 Abnormal electrocardiogram taken in a hospital after digitalis was administered

intervals. It was interpreted as showing evidence of myocardial disease, and the claimant was considered disabled. A slightly greater digitalis effect is noted in a later tracing. Here, the consultant for the insurance company was so suspicious that he telephoned the referring physician and was assured that the claimant had not received digitalis. Still skeptical, he concluded his report, "If the patient is not taking digitalis, I would say that he is totally disabled."

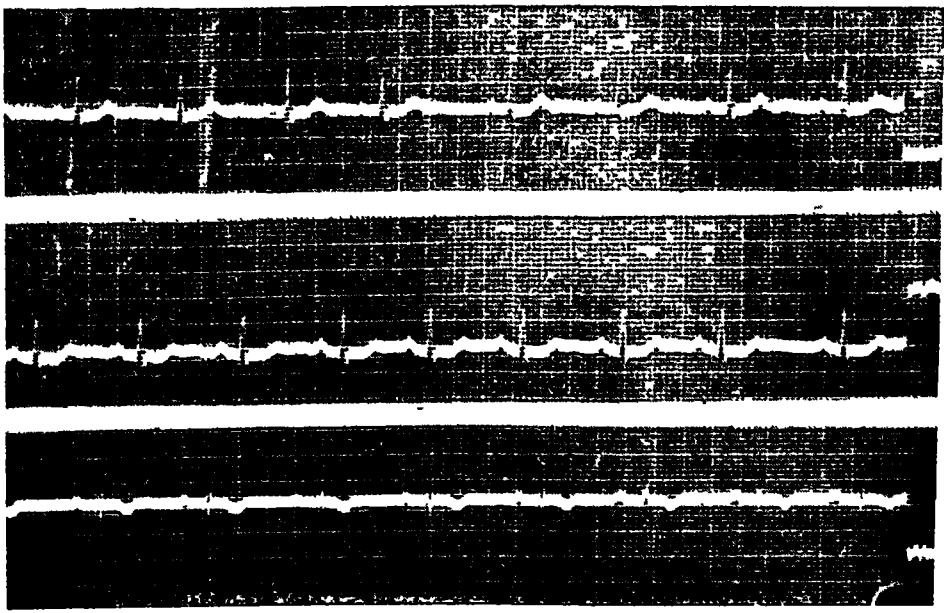


FIG 7 Case 3 Taken by representative of insurance company who regarded myocardial damage as slight—indicative of minor digitalis effects

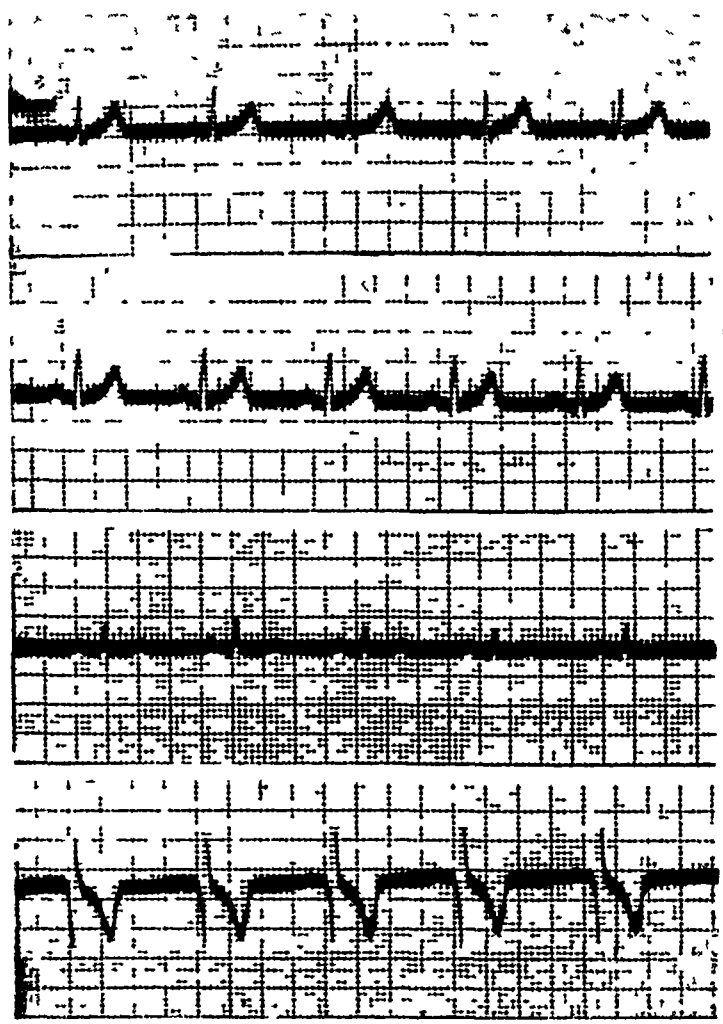


FIG 8 Case 3 Normal electrocardiogram obtained after confession

In figure 4, the ST intervals in Leads I and II are depressed, the T-wave in Lead II appears to be diphasic owing to the depression of the ST segment, and the T-wave in Lead III appears inverted for the same reason. There is also a rather deep Q-wave in Lead III. These findings were interpreted by a physician in the home office of a life insurance company. "It is conceivable that digitalis may cause the changes noted in the conventional and precordial leads, but highly unlikely. Since digitalis administration has been denied, it must be assumed that this record is associated with myocardial damage of coronary origin."

This claimant subsequently confessed participation in this fraud, and a physician admitted having given him digitalis and having coached him in the symptoms of heart disease. Figure 5, a normal electrocardiogram, was obtained after the claimant had confessed and was awaiting trial. He had not received digitalis for months.

Case 3 White male, aged 42, claimed total disability because of attacks of substernal pain stated to have begun while working in a grocery store in September 1936. He was hospitalized for heart disease in December 1936. During this admission an electrocardiogram (figure 6) was taken. This electrocardiogram shows a partial auriculoventricular block, depressed ST segments in Leads II, III, and the chest lead, and the appearance of inverted T-waves in Lead III and the chest lead, and a diphasic T-wave in Lead II, all due to a pulling down of the ST segments. A diagnosis was made of myocardial damage and dropped beats. The physician subsequently admitted surreptitious digitalization. Figure 7 was taken by a physician representing an insurance company. In his opinion the area of myocardial infarction was small, if existent. The depressions of the ST interval suggest a digitalis effect. Electrocardiogram (figure 8), which was obtained after confession, is entirely normal.

REFERENCE

- 1 HEDLEY, O. F. A heart disease racket (preliminary report on an alleged extensive insurance fraud), Jr Am Med Assoc, 1937, cix, 1B-3B (Organization Section)

RECOGNITION OF INCIPIENT THROMBOANGIITIS OBLITERANS IN YOUNG DRAFTEES *

By WILLIAM E JAESMAN, M D , F A C P , and ROBERT H DURHAM, M D , F A C P , with technical assistance of NICHOLAS P DALLIS, M D ,
Detroit, Michigan

FEW people would question the loyalty and patriotism of the average American. In recent months, however, all of us in the medical profession have seen the occasional young man of the draft age who described symptoms of peripheral vascular disease, just as others talk about trouble with the heart, the lungs, or the gastrointestinal tract, apparently in the hope that he might thus evade military service. When such suggestive peripheral blood vessel symptoms are described, we, as examining physicians, should remember that thromboangitis obliterans can and does occur in young men, and make every effort to rule this disease in or out. It may constitute a definite compensation risk.

This phase of the disease was forcefully brought to our attention by a patient who, though first diagnosed thromboangitis obliterans in 1932, is still receiving partial disability government compensation, because his symptoms supposedly began during his service in the First World War.

When the draft boards refer men for special investigation because of a history of suspicious peripheral vascular symptoms, we now follow a special routine of study for the recognition of early or incipient stages of thromboangitis obliterans. This means before the usual criteria for diagnosis are present, namely, intermittent claudication, erythromelalgic symptoms, decrease of arterial pulsations, polycythemia, lowered plasma volume and low chloride concentration. Our special routine of study now is the outgrowth of observation and investigation of the peripheral vessels of some 4,000 patients in the past 14 years. These included patients with hypertension, arteriosclerosis, Buerger's disease, multiple sclerosis, retinitis pigmentosa, Raynaud's disease, hypothyroidism, thrombophlebitis and erythromelalgia. The actual number of thromboangitis obliterans cases in this group is not large, 61, but oddly enough, there have been seven in the past seven months, including four reported later, three draftees referred for study and one boy of 19 in the Michigan National Guard.

PLAN OF STUDY

1 Routine Preliminary Examination To begin with, the usual complete physical examination is carried out. Special attention is given to color changes in the skin of the feet when elevated or dependent, and to arterial pulsations, remembering that in the incipient stage of thromboangitis obliterans, the pulses may be normal. History, so valuable in the average

* Received for publication August 3, 1942

patient coming for medical attention, should not be relied upon too much because of the possibility of willful draft evasion. We also make every effort to exclude arch trouble or foot deformity as the cause for symptoms.

2 Capillaroscopy Our next step is the examination of the capillaries of the skin at the nail fold. The disease under discussion affects arteries, veins and capillaries, and it is our experience that even the early cases show very characteristic capillary changes. Capillaroscopy is described in the literature early in this century especially in foreign medical publications. For example, in 1922 Mueller¹ compared the capillaries in human skin in days of health and illness. In the same year Hagen² described human capillaries under various conditions. In our own country Brown³ described capillaries in Raynaud's disease as early as 1925. Between these early years and the present time there are several other reports on the appearance of human capillaries. To mention a few, Mueller and Parisius⁴ were among the first to call attention to the relation of capillary disorders in neuroses, Griffith⁵ tells of their abnormal appearance in neurasthenic states, Leader⁶ gives us a picture of capillaries in children, Wright⁷ tells of the value of their appearance in various disease conditions, Griffith and Collins⁸ mention capillaries in blood pressure studies, Bordley, Grow and Sherman⁹ describe capillaries in negroes, Olkon¹⁰ tells of their appearance in schizophrenia, Deutsch¹¹ again describes in detail capillaries in Raynaud's disease, and Zondek, Michael and Katz¹² tell of capillaries in myxedema.

The method of capillary study used by the various writers is much the same, but we would refer especially to the method of Duryee and Wright¹³. Our apparatus for viewing capillaries is a simplified model of that described and used by these authors. In addition, we have a comfortable adjustable chair in which the patient is seated with the feet on a movable platform just the height of the microscope stage. The platform may also be placed on a table with the microscope if finger capillaries are to be studied. Light to be reflected from the skin area studied is obtained from a small special bulb and a thin blue glass filter so that only white light is obtained. A resistance coil between the wall plug and the bulb makes it possible to use the regular current.

Because of the greater surface available, the great toes are used. The skin proximal to the nail is gently cleansed with green soap and water and then dried. This is important since even slight irritation may change the appearance of the capillary field. Mineral oil is then applied to the area to be examined. This diminishes the refraction due to unevenness of the outer layer of epithelium.

A metal sleeve or trough on the microscope stage helps to steady the toe, so that the capillaries may be easily studied with the lower power of the microscope and 10x eyepiece. The examination is carried out at room temperature with the patient under as nearly normal resting conditions as possible, usually in the morning but not fasting, and before the use of tobacco that day, or any other substances that might abnormally influence the usual capillary flow or shape.

Naturally one must be very cautious in the interpretation of the capillary loops seen because of a rather wide range of so-called normal. We have already referred above to descriptions of several writers. Our observations, however, have been like those of Leader,⁶ namely, that in normal young



FIG 1 Normal capillary picture at nail bed (Mueller)

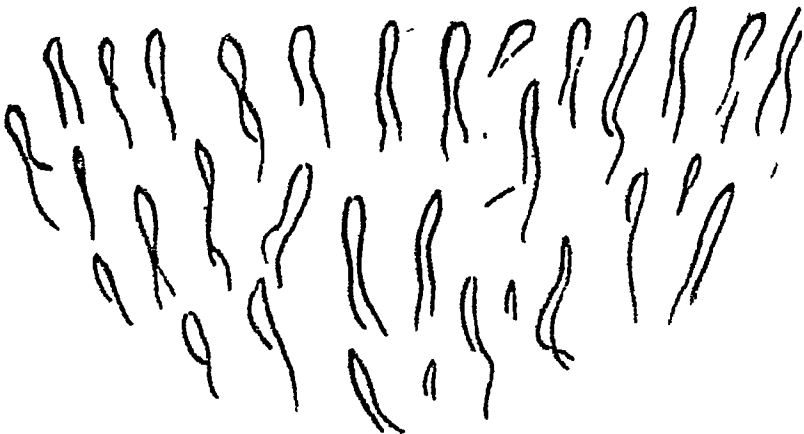


FIG 2 Drawing of capillaries at nail bed of great toe in normal healthy male of 30 years

adults, the distal or terminal capillaries show only slight variations from the expected hairpin-shaped loops, with more or less regular or rhythmic blood flow. Longer and shorter loops are both classed as normal. Figure 1 shows a normal capillary picture at the nail bed in children as described by Mueller. Figure 2 is the picture seen in normal young adults, being a drawing by one of us (N P D) of capillaries as actually observed at the nail fold of the great toes.



FIG 3 Drawing of capillaries at nail bed of great toe in young draftee with early thromboangitis obliterans

When there is impaired blood flow as, for example, in venous stasis or thyroid gland deficiency, there is some dilatation of the capillary loops, but the general shape still follows the normal pattern. But in young men with even early thromboangitis obliterans, other disease conditions being excluded, there is a distinctly different and characteristic picture. Many of the loops are distorted, some showing so-called figure-of-eight tortuosity, others being rosette-shaped, somewhat like a coiled hair. These distorted loops invariably show dilatation and in them the blood flow is sluggish or worm-like. Scattered among these abnormally shaped loops may be some quite normal in shape, but with the arterial side narrowed and showing what is interpreted as spasm, namely, blood cells flowing through in spurts or giving

a segmented or beaded appearance. Then, proximal to the area above described the field is dotted with very short partial loops or "nubbins" as we have termed them. This picture is distinctly different from the usual somewhat tortuous but elongated, thinner-appearing capillaries of arteriosclerosis. Figure 3 illustrates our description of capillaries in early thromboangitis obliterans and figure 4 those in arteriosclerosis. Both are drawings from actual observations, again made by one of us (N P D).

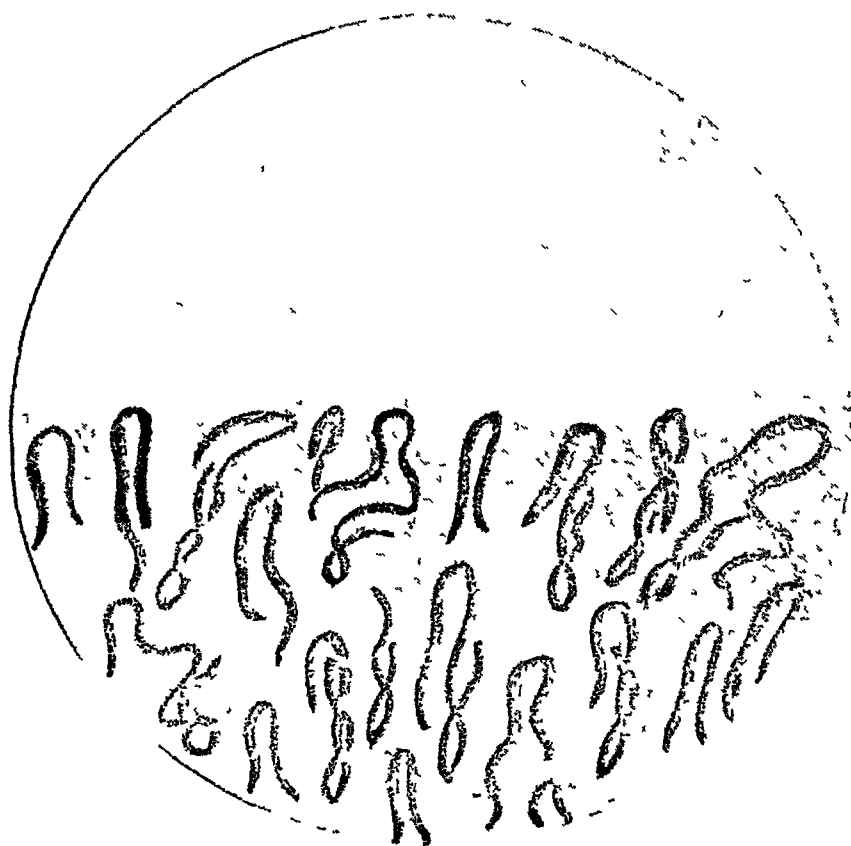


FIG 4 Drawing of capillaries at nail bed of great toe in male of 62 years with arteriosclerosis

We have observed somewhat similar tortuosity with rosette shapes and dilatation in several young patients with multiple sclerosis, but these are more often seen in women, there is no vascular occlusion, and other diagnostic data suffice to exclude thromboangitis obliterans. These were interesting observations, nevertheless, and are to be studied further. We have been able to find only one reference to capillaries in multiple sclerosis.¹⁴

3 Skin Temperature Response to Cold and Heat The next step in our plan of study is to determine if there is any vascular occlusion, by taking skin temperature readings by our modification of the method of Gibbon and Landis^{15, 16}. The patient is placed in a cool room, temperature between 60° and 65° F, with the feet and legs bare, the remainder of the body being kept

comfortably warm with blankets. The same chair is used as for capillary study. After exposure of the feet and legs for half an hour, the skin temperature of the dorsum and great toes is measured thermoelectrically. Temperature readings are repeated at five minute intervals and when a stable temperature level is obtained, one forearm is immersed in water at from 110° to 114° F, in a thermostatically controlled water bath*. Skin temperature readings are again taken at five minute intervals until a maximum rise is reached, or for at least one hour.

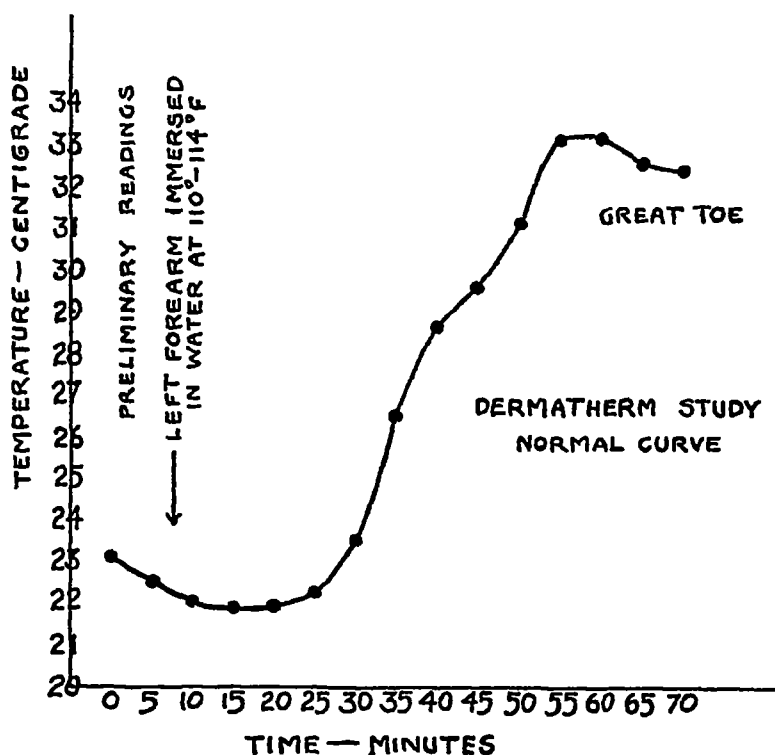


FIG 5 Normal skin temperature response to cold and heat

In the earlier years of our skin temperature studies, readings were taken with the dermaterm after cooling the feet and legs as above, and then after spinal anesthesia. We have selected the modified Gibbon and Landis method, however, because it is much simpler and safer so that it can easily be carried out by a junior assistant, is essentially as satisfactory as spinal anesthesia, and more so than oscillometry.

In the normal or purely functional vasospastic individual, vasodilatation begins within 15 minutes and reaches a maximum of above 32° C—at times 34° C—within one half hour. Such a response excludes the possibility of obliterating structural disease of the arteries. A normal curve of temperature response is shown in figure 5.

* The self-regulating, thermostatically controlled water bath was designed and constructed at the Henry Ford Hospital with the technical assistance of Mr A. Krolicki, Chief of the Maintenance Division.

In thromboangitis obliterans there is invariably evidence of obliteration or occlusion in at least one lower extremity. In early cases such occlusion or diminished ability of the arteries to dilate may be only slight, so that this study is sometimes but not constantly of help in the incipient stage of the disease. This will be shown in the curves of temperature response, or *dermatherm study*, as we call the procedure, in the three draftees and one national guard member mentioned above.

CASE REPORTS

Case 1 F N, a single Jewish draftee of 26 years, was studied because of the complaint of aching in the feet with some sensitiveness of the skin to touch. At times there was also slight aching in the arms and hands. There was bluish discoloration of the skin of the feet in the dependent position. The toes felt cold to the examining hand. Elevation of the legs produced slight but prompt blanching of the skin of the feet. Pulses could not be definitely felt in either the dorsalis pedis or posterior tibial arteries, whereas radial and ulnar pulses were normal bilaterally.

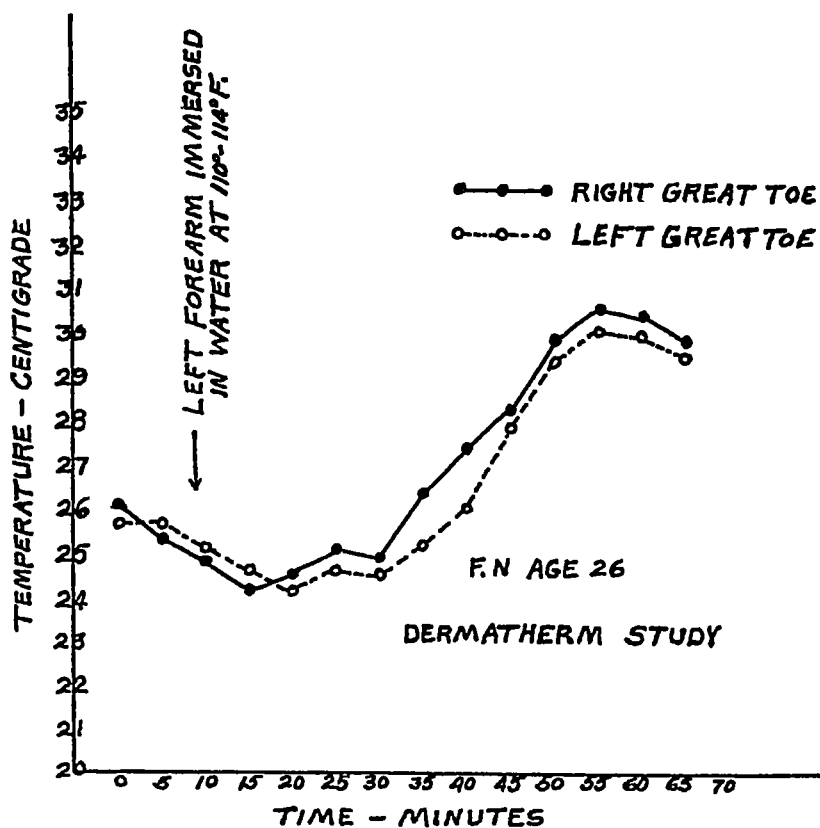


FIG 6 Early case of thromboangitis obliterans

The distal capillaries of the nailfold of the right great toe showed striking tortuosity with some of the loops appearing clumped or in rosette shapes. These were somewhat dilated and blood flow in them was sluggish. Only scattered loops had the normal hairpin shape and in these there was some segmented or beaded flow, evidence of spasm. The left great toe showed a very similar picture except for less dilatation and tortuosity of the terminal capillary loops. On both sides, more proximally there were many of the characteristic short, thickened, partial loops or "nubbins" spoken of above.

Figure 6 shows the result of the dermaterm study in this case. It will be noted that after exposure of the feet and legs in a cool room for 30 minutes the skin temperature level did not drop to as low a level as is often or usually seen. What is more significant, however, is that with heat to one forearm, temperature rise of the skin of the feet was considerably slower than normal or when only vasospasm is present, and also, the total rise was only to a maximum of 30.8°C on the right and to 30.5°C on the left as compared with a normal of from 32° to 33°C . In a young man of this age, apparently well in every other respect, such a response makes us feel very definitely that there is already slight arterial occlusion. With the history, physical and capillary findings, the dermaterm study thus helps in establishing the diagnosis.

Case 2 E. R., a single Jewish diaftee of 25 years, complained of itching of the skin of the hands and feet with occasional twinges of pain in the feet. There was also some sensitiveness to cold.

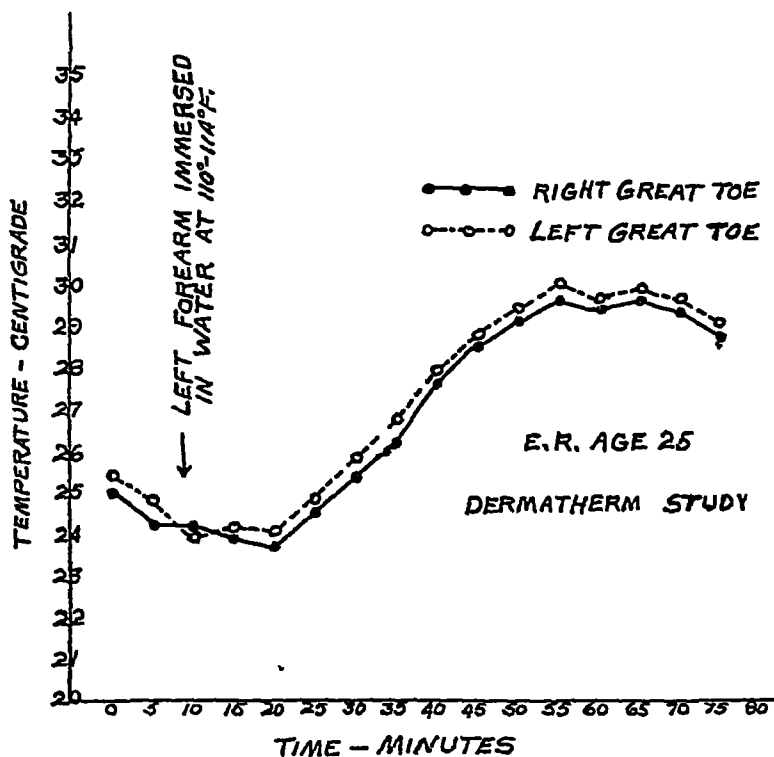


FIG 7 Early case of thromboangitis obliterans

Prompt blanching of the skin of the feet occurred on elevation, but there was no red or blue discoloration when the feet were placed in the dependent position. The pulse was normal in both posterior tibial, but markedly diminished in both dorsalis pedis arteries. Radial pulses were normal.

Capillaries of the right great toe showed moderate tortuosity with occasional rosette shapes and moderate dilatation of the loops with sluggish blood flow. Only slight spasm was noted in the more normally shaped loops occupying about one half of the field. The left great toe showed more tortuosity and clumping of the terminal loops, otherwise it was similar to the right. Again the short "nubbins" were seen in large numbers proximal to the first few distal rows of loops.

The result of the dermaterm study is shown in figure 7. There again is less coldness than is usually seen after exposure in a cool room, the lowest skin temperature reading being 23.6°C . The patient complained of very cold feet at the time and the

skin became very dusky Following immersion of the forearm in warm water there was quite prompt beginning of temperature rise in the skin of the feet, but again delayed and diminished total rise, almost an hour being required for the maximum temperature rise, and this being again below the normal, namely 29.6°C on the right and 30°C on the left

Case 3 H H, a 24-year-old draftee of Irish-American descent, was referred because of pain in the arch of the left foot, occurring when standing, or coming on at times after walking a block or two Shifting his weight to the right foot soon brought relief Symptoms were no worse in cold weather There were none in the right foot or leg, nor the upper extremities

There was quite prompt blanching of the skin on elevating the left leg, less on the right No definite redness or blueness developed with the foot dependent for a time Pulsation was normal in both posterior tibial arteries, just palpable in the right dorsalis pedis and absent in the left

Capillaries of both great toes showed marked tortuosity of the terminal loops for a boy of this age Most loops also showed dilatation with marked stasis of blood flow Here and there were narrowed, normally shaped loops with intermittent and segmented flow, interpreted as spasm Proximal to these loops were numerous incomplete loops or short "nubbins" as in the preceding two cases

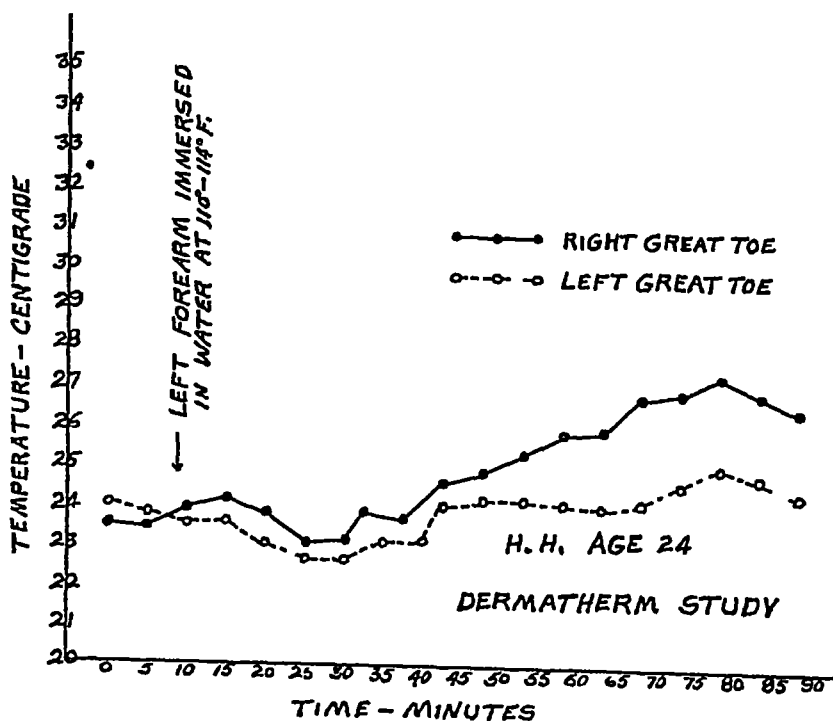


FIG 8 Early case of thromboangitis obliterans

Figure 8 is a graph of the dermatherm study in this case, showing definitely impaired vasodilating ability, more marked in the left, corresponding to the clinical findings There is confirmation of the spasm noted in the capillaries in that there is considerable delay in response to heat Organic occlusion is evident from the small total temperature rise of 3°C on the left and 4.5°C on the right, and a maximum rise to only 25°C on the left and 27.3°C on the right after immersion of one forearm in warm water for more than an hour

Case 4 R C, a single boy of 19 years, English descent, one of our former hospital messenger boys, came for advice because of rather severe cramp-like pain in the

right foot and leg and some aching in the left lower extremity while doing guard duty with the Michigan National Guard. More recently, walking only 100 or 200 yards precipitated severe aching in the right calf muscles. Rest relieved this aching quite promptly. There was also some coldness of the feet, not previously noticed. His habits were good except that he was fond of rye bread and smoked a package of cigarettes daily.

The hands and feet were cold to touch. In the dependent position the skin of the right foot was dusky and elevation produced prompt blanching of the skin. Similar less marked changes were present on the left. Pulsations were easily felt in all the peripheral vessels.

Capillary loops appeared the same at the nailfold of both great toes, being normal in number, but showing considerable dilatation of the distal portion and moderate tortuosity. Some segmentation of the flow was noted giving evidence of spasm. Outstanding again were the numerous short "nubbin-like" loops proximally, considered significant in this case especially because of the absence of arterial occlusion by palpation.

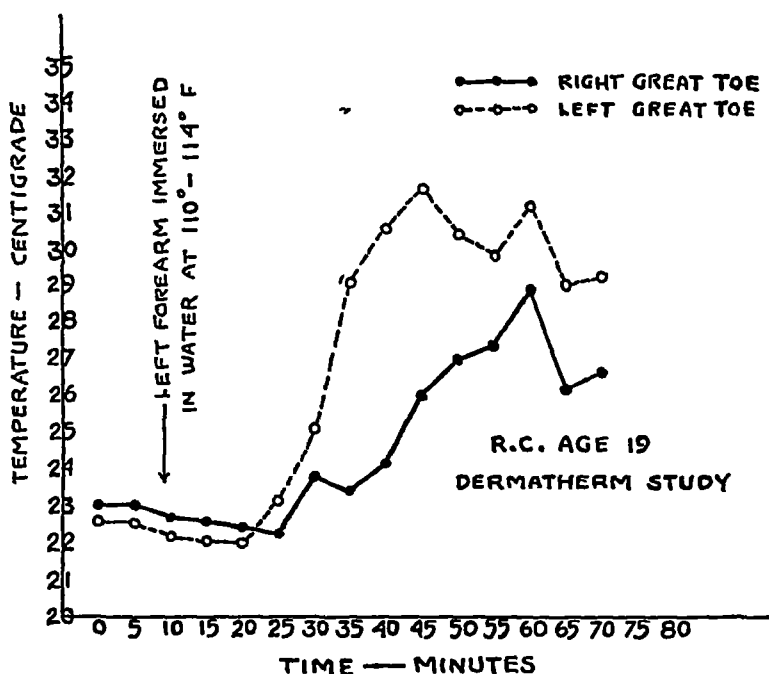


FIG 9 Early case of thromboangitis obliterans

Figure 9 shows rather striking evidence of organic arterial obstruction in the right lower extremity of this patient, even at age 19. It is evidently very early since the maximum temperature rise did reach 29° C. On the left side with only mild symptoms, the rise was still practically normal, 31.5° C. Dermatherm study was felt to be a really important investigation in this case, giving confirmation of our suspicions from the history, the few suggestive physical findings and the capillary findings. It was interesting, too, that abstinence from tobacco made for remarkable improvement in a single week. Despite this response, we always emphasize other significant influencing factors, such as extremes of heat and cold to the feet, ill fitting shoes, careless cutting of callouses or corns, poor habits of eating or resting, and infections of the skin of the feet, particularly trichophytosis.

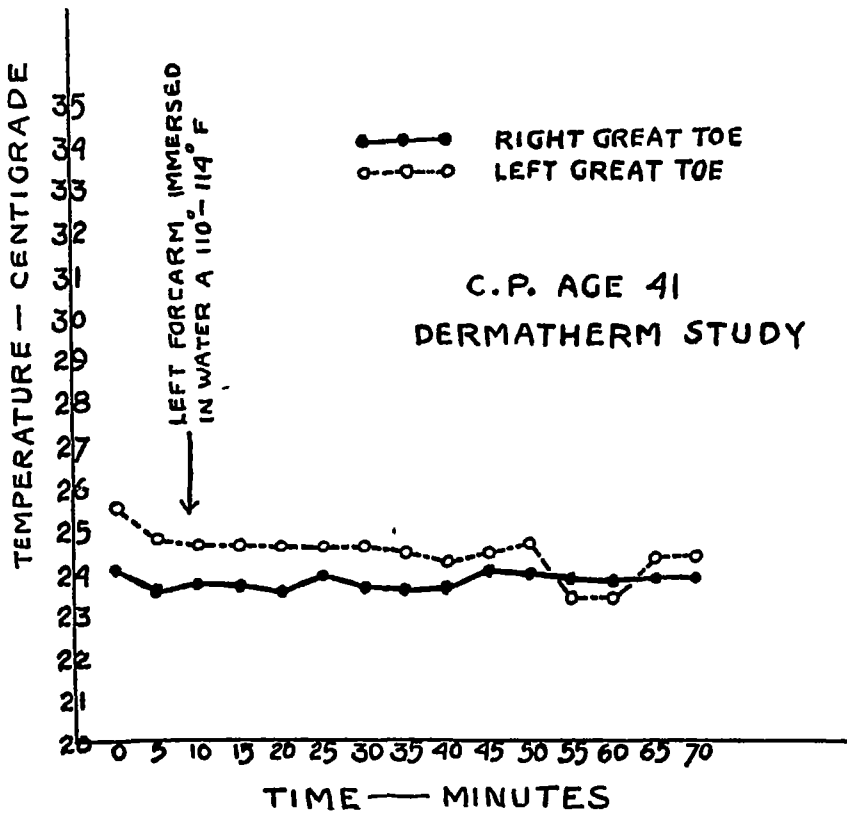


FIG 10 Moderately advanced case of thromboangutis obliterans

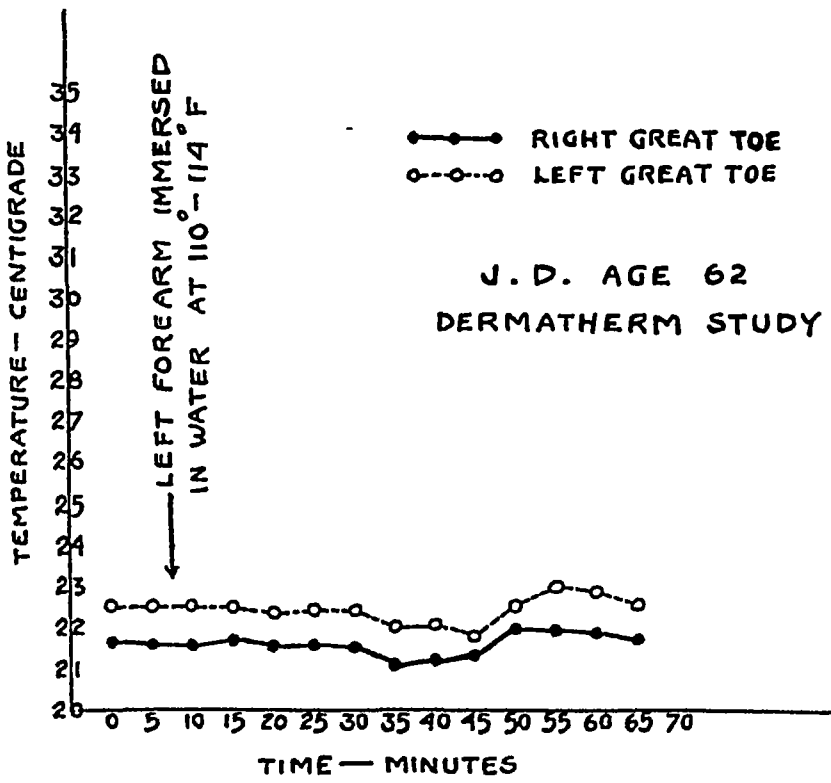


FIG 11 Case of arteriosclerosis obliterans

COMMENT

It will be noted that one foot and leg are invariably more involved than the other, and that a single digit may have symptoms. Yet, at least some involvement of the larger arteries is demonstrated in the slight to moderate organic occlusion revealed by the dermatherm study in each of the four young men reported. None of these cases showed complete occlusion, but such organic obstruction can and does occur in thromboangitis obliterans even as in the older patient with arteriosclerotic occlusion. Of our 61 cases more than one half gave a dermatherm study response like that shown by the curve in figure 10, one of our recent thromboangitis cases, aged 41. This is no different from figure 11 which is the curve of a similar study in a man of 62 years with arteriosclerosis obliterans, but naturally these advanced cases of thromboangitis obliterans require no special study for diagnosis. It is the incipient stage, in a young man between 17 and 21 years of age, in which the diagnosis may be a more difficult problem, and it is in this stage that we have felt the plan outlined to be of definite aid.

SUMMARY AND CONCLUSIONS

1 Thromboangitis obliterans occurs in young draftees and should not be overlooked because of possible long continued disability compensation if such draftees are accepted for active service.

2 Incipient stages of the disease may be recognized from the nailfold capillary picture described, together with a modification of the Gibbon and Landis dermatherm study.

3 In these early stages there is diminution in vasodilatation of mild to moderate degree in at least one lower extremity. In the four cases reported the maximum temperature rise in the most involved extremity, after immersion of a forearm in water at 110° to 114° F, was from 2.5° to 4.8° C below the accepted normal of 32° to 33° C. Later, with more actual occlusion, there is constant coldness of the skin as in arteriosclerosis obliterans and little or no temperature rise on exposure to heat.

4 Two of our patients did not show as low a level of skin temperature as is usually seen after exposure of the feet and legs in a cool room for 30 minutes. We might speculate that with a more active inflammatory process in the vessels in this stage of the disease there might be less vasoconstricting ability. A more likely explanation is the individual differences that are bound to be found in the way of sensitiveness to cold, even with an early disease process present.

5 Having diagnosed the disease early, we should be able to keep these young men reasonably free from symptoms and prevent complications by teaching them more moderate habits of living and meticulous care of the feet.

BIBLIOGRAPHY

- 1 MUELLER, O Die Kapillaren der menschlichen Koeperoberflaeche in gesunden und kranken Tagen, 1922, Ferdinand Enke, Stuttgart
- 2 HAGEN, DR W Periodische konstitutionelle und pathologische Schwankungen im Verhalten der Blut Kapillaren, Arch f path Anat u klin Med, 1922, ccxxxix, 504
- 3 BROWN, G E The skin capillaries in Raynaud's disease, Arch Int Med, 1925, xxxv, 56
- 4 MUELLER, O, and PARISIUS, W Die Blutdruckkrankheit, 1932, Ferdinand Enke, Stuttgart.
- 5 GRIFFITH, J Q, JR The frequent occurrence of abnormal cutaneous capillaries in constitutional neurasthenic states, Am Jr Med Sci, 1932, clxxxiii, 180
- 6 LEADER, S D Capillary microscopy in children, Am Jr Dis Child, 1933, xlv, 403
- 7 WRIGHT, I S Clinical value of human capillary studies in fever, mental deficiency, nephritis, vascular diseases, clubbed fingers, arthritis, tobacco smoking and argyria, Jr Am Med Assoc, 1933, ci, 439
- 8 GRIFFITH, J Q, JR, and COLLINS, L H, JR Method of observing blood pressure by arterial compression and simultaneous capillary observation, Am Heart Jr, 1933, viii, 671
- 9 BORDLEY, J III, GROW, M H, and SHERMAN, W S A note on the nailfold capillaries in negroes, Bull Johns Hopkins Hosp, 1936, lxx, 447
- 10 OLKON, D M Capillary structure in patients with schizophrenia, Arch Neurol and Psychiat, 1939, xlii, 652
- 11 DEUTSCH, FELIX Capillary studies in Raynaud's disease, Jr Lab and Clin Med, 1941, xxvi, 1729
- 12 ZONDEK, H, MICHAEL, M, and KATZ, A The capillaries in myxedema, Am Jr. Med Sci, 1941, ccii, 435
- 13 DURYEE, W, and WRIGHT, I S Present day technique for the study of human capillaries, Am Jr Med Sci, 1923, clxxxv, 664
- 14 GOMIRATO, G . A study of capillary alterations in multiple sclerosis, Riv di patol nerv, 1939, liii, 148
- 15 GIBBON, J H, and LANDIS, E M Vasodilatation in the lower extremities in response to immersing the forearms in warm water, Jr Clin Invest., 1932, xi, 1019
- 16 LANDIS, E M, and GIBBON, J H A simple method of producing vasodilatation in the lower extremities, Arch Int Med, 1933, lxxiii, 785

APPROXIMATE INSULIN CONTENT OF EXTEMPORANEOUS MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN *

By FRANKLIN B PECK, M D , F A C P , *Indianapolis, Indiana*

THE number of possible modifications of insulin is almost unlimited. Within the last few years several new preparations have been described ^{1, 2, 3} and each has seemed to possess certain more or less specific advantages ^{4, 5, 6}. Nevertheless, in common with protamine zinc insulin these modifications must of necessity be prepared with definite proportions of ingredients so each has its own individual time-activity, with onset and duration of physiologic action constant for each fixed combination. Each of these modifications provides a curve of time-activity which fits the needs of a limited group of diabetic patients almost perfectly ⁶. But judging from the experience when protamine zinc insulin was undergoing its original development in this country and combinations containing various proportions of protamine, of zinc and of calcium were applied clinically, it seems doubtful that any single preparation can be developed within the near future having all desirable attributes and combining rapid and prolonged effects. One alternative would be to devise a series of insulin modifications of varying intensity and duration of action, an event that would doubtless result in untold confusion to patients and physicians alike as well as complicating the marketing of preparations containing insulin.

The majority of diabetic patients can be satisfactorily controlled by soluble insulin if enough doses are given, by single doses of protamine zinc insulin if the total insulin requirement is less than 30 or 40 units per day, or by one injection of protamine zinc insulin and one or more supplementary doses of rapidly-acting insulin in event that the case is exceptionally severe. Various expedients of dietary rearrangement have been advocated in stabilizing patients of the latter group, such as unequal apportionment of meals or variation of the usual intervals between meal times, and the provision of small lunches between meals and at bedtime in order more nearly to adapt the inflow of exogenous carbohydrate to the rate at which active insulin is released from the depot injection of insoluble modified insulin. Recently, evidence ^{7, 8, 9} is accumulating that injections of extemporaneously prepared mixtures of insulin and protamine zinc insulin permit more highly individualized readjustment of each case since the patient may employ a modification which is "tailor made" to meet varying requirements of onset and duration of insulin effect.

Hagedorn ¹⁰ and Krarup ¹¹ first pointed out the possibility of altering the time-activity of protamine-insulin in order to obtain both a quick and a

* Received for publication September 21, 1942.

From the Lilly Research Laboratories and Diabetic Clinic, Indianapolis City Hospital

long duration of action. Some special modifications of protamine zinc insulin have been under investigation for several years. These contain more or less protamine in relation to insulin content and have different pH values ranging down to the acid side where there is no precipitate but the combination remains in clear solution. Graham¹² and Lawrence¹³ used extemporaneous mixtures clinically and reported favorable results, but early experience in this country was not encouraging, probably because the mixtures consisted of too small a proportion of unmodified insulin to protamine zinc insulin. Watson¹⁴ in Canada and Wauchope¹⁵ in England compared the effectiveness of mixtures in patients treated alternately by means of separate injections and then with mixtures. The conclusions were that separate injections of unmodified and protamine zinc insulin led to better control and more economical and accurate balancing. Later Wilder⁷ successfully adapted the method, and Ulrich⁸ pointed out that by adding sufficiently large amounts of unmodified insulin to protamine zinc insulin, a point is reached beyond which some insulin may be expected to remain. He found by trial that approximately three parts of unmodified insulin to two parts of protamine zinc insulin best served his purpose clinically and that the results were no more unpredictable than those obtained following administration of separate doses of either preparation.

Colwell et al.⁹ have developed the method further with more extensive clinical studies and have shown that suitable mixtures of the two standard insulins may be prepared which show any desirable intermediate action, ranging between insulin and protamine zinc insulin in promptness, intensity, and duration of effect. The most generally useful mixture appears to be one made from two parts of insulin to one part of protamine zinc insulin (referred to as a two to one mixture). His series of cases have shown uniform improvement in the number of total injections required, control of glycosuria, avoidance of nocturnal hypoglycemia, and lower average unitage for control.

Because of the wide variability of dietary management in different clinics,

TABLE I

Insulin Protamine Zinc Insulin Mixtures		Approximate Content of Rapidly-Acting Insulin	
Parts			
Insulin	Protamine Zinc Insulin	%	
1	3	=	10
1	2	=	15
1	1	=	25
3	2	=	40
2	1	=	50
3	1	=	65
4	1	=	70
5	1	=	75

as well as variations in individual patients, it is probable that no single fixed proportion will be found suitable for the treatment of all cases. The purpose of this report is to make available some quantitative data that have been accumulated. Peck¹⁸ recently emphasized that the curve of soluble insulin content of such mixtures lies in a zone which may be somewhat variable under the conditions existing when mixtures are prepared extemporaneously. Table 1 gives the approximate zone of insulin content of insulin-protamine zinc insulin mixtures which have been adjusted to the approximate pH of protamine zinc insulin by buffering. Thus far this is the only practical method of assay. In the table the actual figures have been adjusted to the nearest round number. Table 2 is based on these figures and is more useful clinically.

TABLE II

APPROXIMATE UNITAGE IN MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN

1:①				3:②				2:①				3:①				
UNITS TOTAL	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed
10	5	5	= 2.5	7.5	6	4	= 4	6	7	3	= 5	5	7.5	2.5	= 6.5	3.5
15	7.5	7.5	= 4	11	9	6	= 6	9	10	5	= 7.5	7.5	11	4	= 10	5
20	10	10	= 5	15	12	8	= 8	12	13	7	= 10	10	15	5	= 13	7
25	12.5	12.5	= 6	19	15	10	= 10	15	17	8	= 12.5	12.5	19	6	= 16	9
30	15	15	= 7.5	22.5	18	12	= 12	18	20	10	= 15	15	22.5	7.5	= 19.5	10.5
35	17.5	17.5	= 9	26	21	14	= 14	21	23	12	= 17.5	17.5	26	9	= 23	12
40	20	20	= 10	30	24	16	= 16	24	27	13	= 20	20	30	10	= 26	14
45	22.5	22.5	= 11	34	27	18	= 18	27	30	15	= 22.5	22.5	34	11	= 29	16
50	25	25	= 12.5	37.5	30	20	= 20	30	33	17	= 25	25	37.5	12.5	= 32.5	17.5
60	30	30	= 15	45	36	24	= 24	36	40	20	= 30	30	45	15	= 39	21
70	35	35	= 17.5	52.5	42	28	= 28	42	47	23	= 35	35	52.5	17.5	= 45.5	24.5
80	40	40	= 20	60	48	32	= 32	48	53	27	= 40	40	60	20	= 52	28
90	45	45	= 22.5	67.5	54	36	= 36	54	60	30	= 45	45	67.5	22.5	= 58.5	31.5
100	50	50	= 25	75	60	40	= 40	60	67	33	= 50	50	75	25	= 65	35
110	55	55	= 27.5	82.5	66	44	= 44	66	73	37	= 55	55	82.5	27.5	= 71.5	38.5
120	60	60	= 30	90	72	48	= 48	72	80	40	= 60	60	90	30	= 78	42
130	65	65	= 32.5	97.5	78	52	= 52	78	87	43	= 65	65	97.5	32.5	= 84.5	45.5
140	70	70	= 35	105	84	56	= 56	84	93	47	= 70	70	105	35	= 91	49
150	75	75	= 38	112	90	60	= 60	90	100	50	= 75	75	112.5	37.5	= 97.5	52.5

as one can determine from it at a glance the approximate relative proportion of rapidly-acting and slowly-acting insulin that will be present in a given mixture *

* This does not necessarily infer that the time-activity of the quick-acting component is identical with that of standard preparations of unmodified insulin as marketed, likewise, the time-activity of the precipitated component may not be identical with that of standard preparations of protamine zinc insulin.

long duration of action Some special modifications of protamine zinc insulin have been under investigation for several years These contain more or less protamine in relation to insulin content and have different pH values ranging down to the acid side where there is no precipitate but the combination remains in clear solution Graham¹² and Lawrence¹⁸ used extemporaneous mixtures clinically and reported favorable results, but early experience in this country was not encouraging, probably because the mixtures consisted of too small a proportion of unmodified insulin to protamine zinc insulin Watson¹⁴ in Canada and Wauchope¹⁵ in England compared the effectiveness of mixtures in patients treated alternately by means of separate injections and then with mixtures The conclusions were that separate injections of unmodified and protamine zinc insulin led to better control and more economical and accurate balancing Later Wilder⁷ successfully adapted the method, and Ulrich⁸ pointed out that by adding sufficiently large amounts of unmodified insulin to protamine zinc insulin, a point is reached beyond which some insulin may be expected to remain He found by trial that approximately three parts of unmodified insulin to two parts of protamine zinc insulin best served his purpose clinically and that the results were no more unpredictable than those obtained following administration of separate doses of either preparation

Colwell et al⁹ have developed the method further with more extensive clinical studies and have shown that suitable mixtures of the two standard insulins may be prepared which show any desirable intermediate action, ranging between insulin and protamine zinc insulin in promptness, intensity, and duration of effect The most generally useful mixture appears to be one made from two parts of insulin to one part of protamine zinc insulin (referred to as a two to one mixture) His series of cases have shown uniform improvement in the number of total injections required, control of glycosuria, avoidance of nocturnal hypoglycemia, and lower average unitage for control

Because of the wide variability of dietary management in different clinics,

TABLE I

Insulin Protamine Zinc Insulin Mixtures		Approximate Content of Rapidly-Acting Insulin	
Parts			
Insulin	Protamine Zinc Insulin	%	
1	3	=	10
1	2	=	15
1	1	=	25
3	2	=	40
2	1	=	50
3	1	=	65
4	1	=	70
5	1	=	75

as well as variations in individual patients, it is probable that no single fixed proportion will be found suitable for the treatment of all cases. The purpose of this report is to make available some quantitative data that have been accumulated. Peck¹⁰ recently emphasized that the curve of soluble insulin content of such mixtures lies in a zone which may be somewhat variable under the conditions existing when mixtures are prepared extemporaneously. Table 1 gives the approximate zone of insulin content of insulin-protamine zinc insulin mixtures which have been adjusted to the approximate pH of protamine zinc insulin by buffering. Thus far this is the only practical method of assay. In the table the actual figures have been adjusted to the nearest round number. Table 2 is based on these figures and is more useful clinically

TABLE II

APPROXIMATE UNITAGE IN MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN

1:①				3:②				2:①				3:①				
UNITS TOTAL	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed	Insulin	P.Z.I	Quick	Pro longed
10	5	5	= 2.5	7.5	6	4	= 4	6	7	3	= 5	5	7.5	2.5	= 6.5	3.5
15	7.5	7.5	= 4	11	9	6	= 6	9	10	5	= 7.5	7.5	11	4	= 10	5
20	10	10	= 5	15	12	8	= 8	12	13	7	= 10	10	15	5	= 13	7
25	12.5	12.5	= 6	19	15	10	= 10	15	17	8	= 12.5	12.5	19	6	= 16	9
30	15	15	= 7.5	22.5	18	12	= 12	18	20	10	= 15	15	22.5	7.5	= 19.5	10.5
35	17.5	17.5	= 9	26	21	14	= 14	21	23	12	= 17.5	17.5	26	9	= 23	12
40	20	20	= 10	30	24	16	= 16	24	27	13	= 20	20	30	10	= 26	14
45	22.5	22.5	= 11	34	27	18	= 18	27	30	15	= 22.5	22.5	34	11	= 29	16
50	25	25	= 12.5	37.5	30	20	= 20	30	33	17	= 25	25	37.5	12.5	= 32.5	17.5
60	30	30	= 15	45	36	24	= 24	36	40	20	= 30	30	45	15	= 39	21
70	35	35	= 17.5	52.5	42	28	= 28	42	47	23	= 35	35	52.5	17.5	= 45.5	24.5
80	40	40	= 20	60	48	32	= 32	48	53	27	= 40	40	60	20	= 52	28
90	45	45	= 22.5	67.5	54	36	= 36	54	60	30	= 45	45	67.5	22.5	= 58.5	31.5
100	50	50	= 25	75	60	40	= 40	60	67	33	= 50	50	75	25	= 65	35
110	55	55	= 27.5	82.5	66	44	= 44	66	73	37	= 55	55	82.5	27.5	= 71.5	38.5
120	60	60	= 30	90	72	48	= 48	72	80	40	= 60	60	90	30	= 78	42
130	65	65	= 32.5	97.5	78	52	= 52	78	87	43	= 65	65	97.5	32.5	= 84.5	45.5
140	70	70	= 35	105	84	56	= 56	84	93	47	= 70	70	105	35	= 91	49
150	75	75	= 38	112	90	60	= 60	90	100	50	= 75	75	112.5	37.5	= 97.5	52.5

as one can determine from it at a glance the approximate relative proportion of rapidly-acting and slowly-acting insulin that will be present in a given mixture *

* This does not necessarily infer that the time-activity of the quick-acting component is identical with that of standard preparations of unmodified insulin as marketed, likewise, the time-activity of the precipitated component may not be identical with that of standard preparations of protamine zinc insulin

Clinical experience thus far indicates that the most generally useful extemporaneous mixtures are in the ratio of three to two or two to one parts of insulin to protamine zinc insulin. For practical purposes, mixtures made of equal parts do not show effects significantly different in action from those obtained when using protamine zinc insulin whereas the combinations containing three parts of insulin to one part of protamine zinc insulin result in too short a time-activity and too great an intensity of effect during the day-time. The table of approximate unitage provides a quantitative starting point which we have found useful in making individual readjustments in the direction of greater or lesser insulin activity and duration of effect. These figures are to be regarded as only approximate, several factors may be responsible for variation in either direction. For example, the pH may vary somewhat in different mixtures depending upon the relative amounts of the different preparations used and this may affect the total solubility of the mixture in the tissues. Furthermore, not all patients may be anticipated to respond in an identical manner. There may also be differences in the results obtained when shifting from one manufacturer's lot to another or, more particularly, when using preparations of different manufacturers since these may not always be chemically and physically identical. For these reasons, the greatest consistency of results should be gained by using the same product in the same proportions, and to simplify matters still further, in the same concentrations.

SUMMARY

Two tables are presented to show the approximate range of insulin content in mixtures of insulin and protamine zinc insulin which have been extemporaneously prepared.

It is emphasized that these figures are approximations only and that variations may occur depending upon individual circumstances. These data should be regarded as only a starting point in making individual readjustments of patients.

REFERENCES

- 1 BISCHOFF, F. Histone combinations of the protein hormones, *Am Jr Physiol*, 1936, cxvii, 182-187.
- 2 REINF, L., SEARLE, D. S., and LANG, E. H. Insulin preparations with prolonged activity, I. Globin insulin, *Proc Soc Exper Biol and Med*, 1939, xl, 171.
- 3 WARVEL, J. H. Protamine and other slow acting insulins and their clinical application, Review of medical progress, *Ohio State Univ Coll of Med*, 1940, p. 140.
- 4 BAUMAN, L. Clinical experience with globin insulin, *Am Jr Med Sci*, 1939, cxcviii, 475-481.
- 5 BARNS, C. A., CUTTLE, T. D., and DUNCAN, G. G. Histone zinc insulin—its pharmacologic characteristics and its application in the treatment of diabetes mellitus, *Jr Pharmacol and Exper Therap*, 1941, lxxii, 331-343.
- 6 BAILLY, C. C. and MARMIE, A. Histone zinc insulin, globin (zinc) insulin and clear protamine zinc insulin. A comparative study of their action, *Jr Am Med Assoc*, 1942, cxviii, 683-690.

- 7 WILDER, R M Clinical diabetes and hyperinsulinism, 1940, W B Saunders Co, Philadelphia, p 92
- 8 ULRICH, HELMUTH Clinical experiments with mixtures of standard and protamine zinc insulin, ANN INT MED, 1941, xiv, 1166-1179
- 9 COLWELL, A R, IZZO, J L, and STRYKER, W A Intermediate action of mixtures of soluble insulin and protamine zinc insulin, Arch Int Med, 1942, lxi, 931-951
- 10 HAGEDORN, H C, JENSEN, B N, KRARUP, N B, and WODSTRUP, I Protamine insulinate, Acta med Scandinav, Supp, 1936, lxxviii, 678-684
- 11 KRARUP, N B Clinical investigations into the action of protamine insulinate, 1935, G E C Gad, Copenhagen
- 12 GRAHAM, G Use of a mixture of ordinary and protamine insulin, Acta med Scandinav, Supp, 1938, xc, 54-63
- 13 LAWRENCE, R D Zinc-protamine-insulin in diabetes Treatment by one daily injection, Brit Med Jr, 1939, i, 1077-1080
- 14 WATSON, E M Comparative efficacy of various methods for administering insulin, Canad Med Assoc Jr, 1940, xliii, 444-447
- 15 WAUCHOPE, G M Zinc protamine insulin and soluble insulin, interaction in combined doses, Lancet, 1940, i, 963-966
- 16 PECK, F B Action of insulin, Proc Am Diabetic Assoc, 1942, ii, 69-83

THE EFFECTIVENESS OF REPLACEMENT THERAPY IN ACHLORHYDRIA *

By ALFRED E KOEHLER, M D , P H D , and EMANUEL WINDSOR, M S ,
Santa Barbara, California

THE diminution or absence of hydrochloric acid in the stomach is not an infrequent occurrence. Among representative studies are those of Bennett and Ryle,¹ who in 1921 observed that 4 per cent of 100 normal, healthy male medical students had achlorhydria, and those made by Vanzant, Alvarez and associates² who in 1932 found achlorhydria in patients without gastric disease in from 25 to 35 per cent between the ages of 60 to 70 years. More recently Ruffin and Dick³ studied the gastric acidity of 2877 patients and found lack of acid in 10 per cent of the total and in 25 to 30 per cent of patients over 45.

Although anacidity may occur in persons with no demonstrable gross disturbances in health at the time, it is a matter of observation that it frequently is associated with varied types of functional or organic abnormalities, particularly digestive disturbances and defective alimentation. The rôle that stomach acid plays in normal physiology has frequently been reviewed and the more outstanding functions may briefly be mentioned as pepsin activation, protein swelling, bactericidal effect, motor and secretory activation, and solution of iron. Recently Ivy and associates⁴ have shown the important effect of lack of acid on calcium absorption and bone growth after gastrectomy in young dogs. The question of degradation of thiamine in the anacid stomach has also been recently raised.

It was, of course, natural that replacement therapy with hydrochloric acid should be considered as an ideal solution of this deficiency problem and dilute hydrochloric acid has been widely used in the attempt to correct anacidity. That little was accomplished by the official pharmacopeial dosage of 10 to 15 minims or 1 c c with meals was, however, becoming rapidly apparent to various observers. Hurst was one of the first to recognize the inadequacy of the usual dosage and recommended 4 to 6 c c. This amount, however, is generally considered impractical and it is the common experience that patients will refuse to take it for any length of time. Crohn⁵ and Kern, Rose and Austin⁶ have shown that the usual doses of dilute hydrochloric acid are ineffective in appreciably modifying the gastric acidity in achlorhydria. The detrimental effects of large doses of hydrochloric acid on the system in general, on the kidneys, and particularly on the teeth, as recently discussed by Staphne,⁷ have been duly considered. In regard to renal irritation and systemic effects it must be recalled that the normal

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942.

From the Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, California.

stomach acid, although secreted in far greater amounts than any therapeutic dose ever suggested, is neutralized, resynthesized and resecreted in a cycle whereas orally administered hydrochloric acid is wholly excreted and in absence of good excretion may be accumulated

Various suggestions have been made to overcome the disagreeable and detrimental effects of oral hydrochloric acid administration, and to this end glutamic acid hydrochloride which can be taken in capsules has been used Shay and Gershon-Cohen⁸ reaffirmed the ineffectiveness of as much as 80 drops (about 5 c c) of dilute hydrochloric acid when added to the usual Ewald meal (20 gm Zweiback in 300 c c water) on the titratable acidity and pH of the stomach contents in patients with anacidity These authors, however, found that four 310 mg capsules of glutamic acid hydrochloride lowered the gastric pH to about 2.5 in two cases It must be borne in mind, however, that such a "meal" of 20 gm Zweiback contains only 3 gm protein and in no way compares with the average largest meal of a day of about 40 gm or even as much as 60 gm protein

The use of citric acid (1 dram powder dissolved in 60–100 c c water, or 60 c c of lemon juice has been advocated by Sansum and Gray⁹ instead of hydrochloric acid This organic acid has the advantage, particularly in the form of lemon juice, of being more palatable and of being subsequently destroyed in the body, thus avoiding renal irritation and the possibility of systemic acidosis No data are available, however, on the effectiveness of this form of replacement as far as the specific physiological functions of normal acidity are concerned

PURPOSE OF STUDY

Our approach to this problem has been to evaluate acid replacement therapy from the standpoint of the actual lowering of the pH in the presence of a *normal meal* and the effectiveness of such lowering as related to several of the known physiological functions of normal gastric acidity In this respect we have studied the effect of replacement therapy on pepsin activation, protein swelling, bactericidal action, calcium solubility and restoration of normal gastric pH

METHODS

The test meal was selected from the standpoint of duplication of a normal meal and of precise reproducibility Table 1 gives the composition of the meal used The ingredients were ground twice in a fine food chopper to a semifluid state The mixture in a vessel was placed in a constant temperature water bath at 37.5° C and agitated by an electric stirrer The calomel and glass electrodes for pH determinations were submerged in the mixture and connected with extended shielded cables to a Beckman pH meter corrected to read at 37.5° C The various acids were then added gradually in small amounts from a burette and repeated pH readings made until constant values were obtained before more was added

TABLE I
Special Test Meal, 558 Calories

Food	Gm	Carbohydrate	Protein	Fat
		gm	gm	gm
Milk	240	12 0	7 2	9 6
Bread	32	16 0	3 2	
Meat (lean ground steak)	100		20 0	9 2
Beans (canned green string)	100	6 0	2 5	
Peaches (juice packed)	100	9 2		
Potato (baked)	100	18 0	3 2	
Water	100			
Total	772	61 2	36 1 *	18 8

* Actual protein found 40 8 gm

Such experiments in vitro have certain advantages over ingestion and aspiration tests, for reproducible curves with large numbers of readings can be obtained and the complicating factor of loss of unknown amounts through the pylorus is avoided. Two factors, however, are not taken into account, the effect of mucin secretion by the stomach mucosa, and the possible regurgitation of alkaline duodenal contents. Both of these factors, however, one by buffer effect and the other by neutralization would tend to require increased amounts of acid in vivo and consequently the amount of added acid to bring about a certain lowering of pH may even be greater than in vitro experiments indicate.

RESULTS

The Effect of Acid Addition to a Normal Meal and Its Relation to Normal Gastric pH and Pepsin Activity The effect of added acid on the pH of a normal meal is shown in figure 1, on which is also shown the normal gastric post-meal pH range of 1.6 to 1.8 (Shohl and King,¹⁰ Haggard and Greenberg¹¹). Our findings showed that with the normal test meal one half to one and a half hours after its ingestion the pH of aspirated gastric contents in eight normal cases ranged from pH 1.4 to 1.8. It is readily seen from our titration curves that no amount of acid that can practicably be taken will lower the pH of a meal to normal levels. No amounts of glutamic acid hydrochloride, citrus acid or lemon juice used reached this range. It took 104 c.c. normal hydrochloric acid which are approximately equivalent to 34 c.c. or 510 drops of dilute hydrochloric acid U.S.P. to bring the meal pH to the normal physiological level. Even the large doses of 5 c.c. of Hurst and Shay and Gershon-Cohen brought the pH of the meal down to only 4.3.

PEPTIC ACTIVATION

That pepsin is only active at low pH values has long been known. On figure 1 is indicated the relation of pH to peptic activity at 37.5° C. on egg albumin as obtained by the Mett tube method. These values are very simi-

lar to those obtained by Northrop¹² measuring amino nitrogen liberation. The optimum peptic activity varies somewhat with various proteins, depending upon their isoelectric points, but the effect of different acids is nearly altogether dependent upon their hydrogen ion dissociation. It is readily seen from the chart that acid substitution therapy in practical amounts can in no way bring about the activation of pepsin.

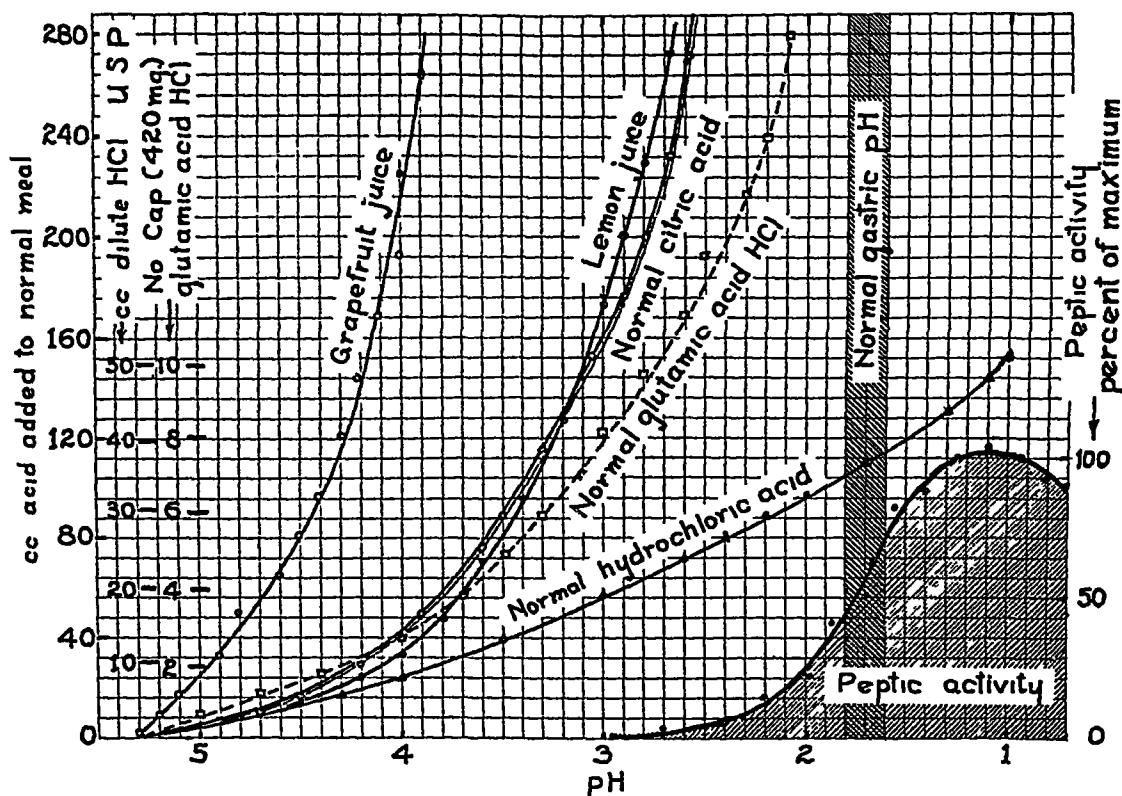


FIG 1 The relationship of the addition of acid to a representative meal and the resultant pH. The relationship of peptic activity to pH and the normal post-meal gastric pH range are also superimposed on this figure.

Relation of Amount of Acid Required to Protein Concentration of Meal

The reason for the large amount of acid necessary to bring the pH of a meal to the normal gastric post-feeding pH is, of course, the buffer capacity of the meal. Carbohydrate and fat have relatively little buffer value and consequently this effect is due largely to the protein content. Figure 2 shows the amount of hydrochloric acid required to bring 100 gm of different ground foods in 100 cc water to various pH values. It will be noticed that, as would be expected, the amount of acid necessary to bring about a certain change for different foods varies greatly, from 2.5 to 34 cc 1.0 normal acid or approximately 0.8 to 11 cc U.S.P. acid. Figure 3 illustrates the relationship of acid to protein by showing the amount of acid required to bring 100 gm of various foods to pH 2.0 as obtained from the data of figure 2. The

amount of acid required is practically a linear function of the protein concentration regardless of the nature of the foodstuff. This relationship emphasized the necessity of the use of a normal meal or at least the protein equivalent of a normal meal to study acid replacement effectiveness. The Ewald test meal of 20 gm Zweiback with a protein content of 3 gm as used by Shay and Gershon-Cohen in their replacement studies gives a highly erroneous impression inasmuch as the average large meal of the day contains from 40 to 60 gm protein. Consequently it would take from 13 to 20 times greater an amount of hydrochloric acid or glutamic acid hydrochloride than these authors found for effective therapy.

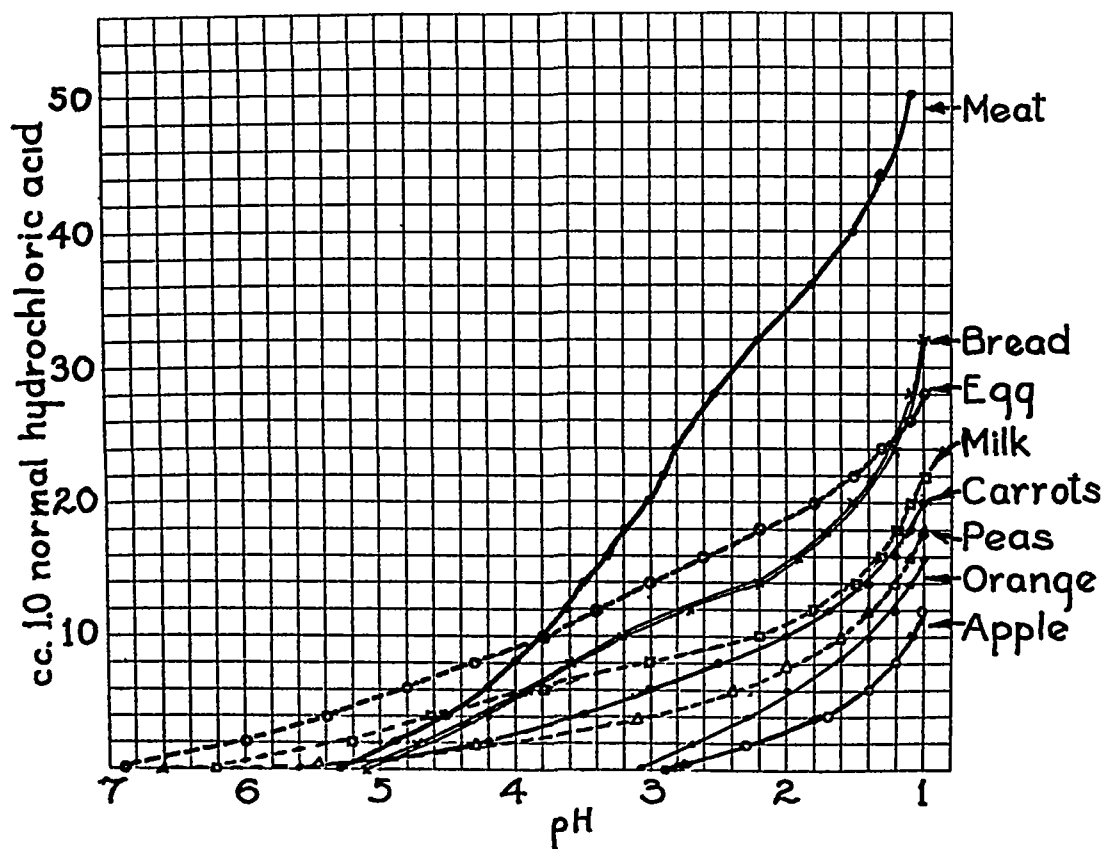


FIG 2 The pH values of 100 gm of various foods brought about by the addition of various amounts of hydrochloric acid

The Effect of pH on Protein Swelling That acids cause hydration and swelling of protein colloids has long been known. It is believed that such hydration and swelling facilitate solution and the penetration of the digestive enzymes. Loeb¹³ has shown that the degree and maximum swelling of a protein in acid solution is proportional to the hydrogen ion concentration. Pure gelatine, for example, was found to have a maximum swelling at pH 3.2 and a minimum at its isoelectric point of 4.7. In figure 4 is presented the relative swelling of commercial gelatine and casein, of unpurified coagulated egg albumin, and the test meal used in our studies. The meal, egg albumin

and casein had a maximum swelling that coincided approximately with the pH of the contents of the normal post-meal stomach. Commercial gelatin had a maximum swelling at pH 3.0 which is a little lower than that found by Loeb (32) for pure gelatin. It is to be noted that the proteins had a minimal swelling (least desirable for digestion) at approximately their isoelectric points, pH 4.0 to 5.0, and the minimal volume for the meal solids also fell within this range. This pH range is about that obtained by the usual acid doses in replacement therapy in achlorhydria with a normal meal and, consequently, as far as swelling is concerned, the usual acid therapy may actually retard digestion. The normal post-meal stomach contents have a pH that gives optimal protein swelling, and replacement therapy to have a maximal effect would have to lower the pH below 2.0.

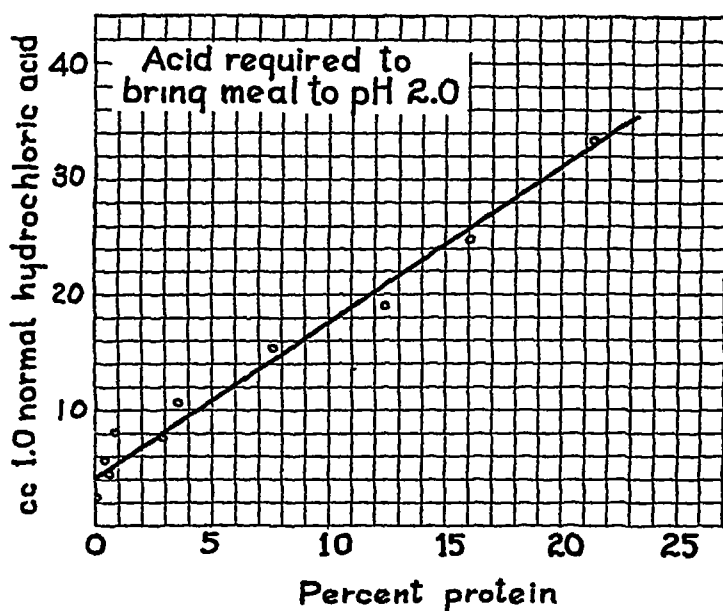


FIG 3 The acid required to bring the pH of 100 gm of various foods of different protein content to pH 2.0

Bactericidal Effect * An extensive study of the bactericidal effect of the gastric acidity has not been undertaken. No attempt was made to study the resistance of especially acid resistant strains of organisms, spores, or lipid encapsulated bacteria, as for example, the tubercle bacillus type. A few of the common organisms were, however, tested to show the acid effect. The standard meal was brought to various pH values with 0.1 N hydrochloric acid as described above. Small aliquots were taken at the different pH values, and to these 0.5 to 1.0 cc of 24 hour broth cultures of the various organisms were added. After mixing the specimens were incubated at 37° C for three hours. Loopfuls of material were then streaked on sterile one sixth blood agar plates. No growth is indicated as 0 and heavy growth as + + + + in table 2.

* The bacteriological work was done by Mrs. Elsie Ferrell

It will be noted that for certain organisms as *E coli*, only pH values materially below 2.0 on 3 hour incubation had any marked destructive effect. Since three hours or less is about the average length of time that food remains in the stomach, it seems that a complete lowering of the pH of the stomach contents to normal levels may be necessary for complete or nearly complete

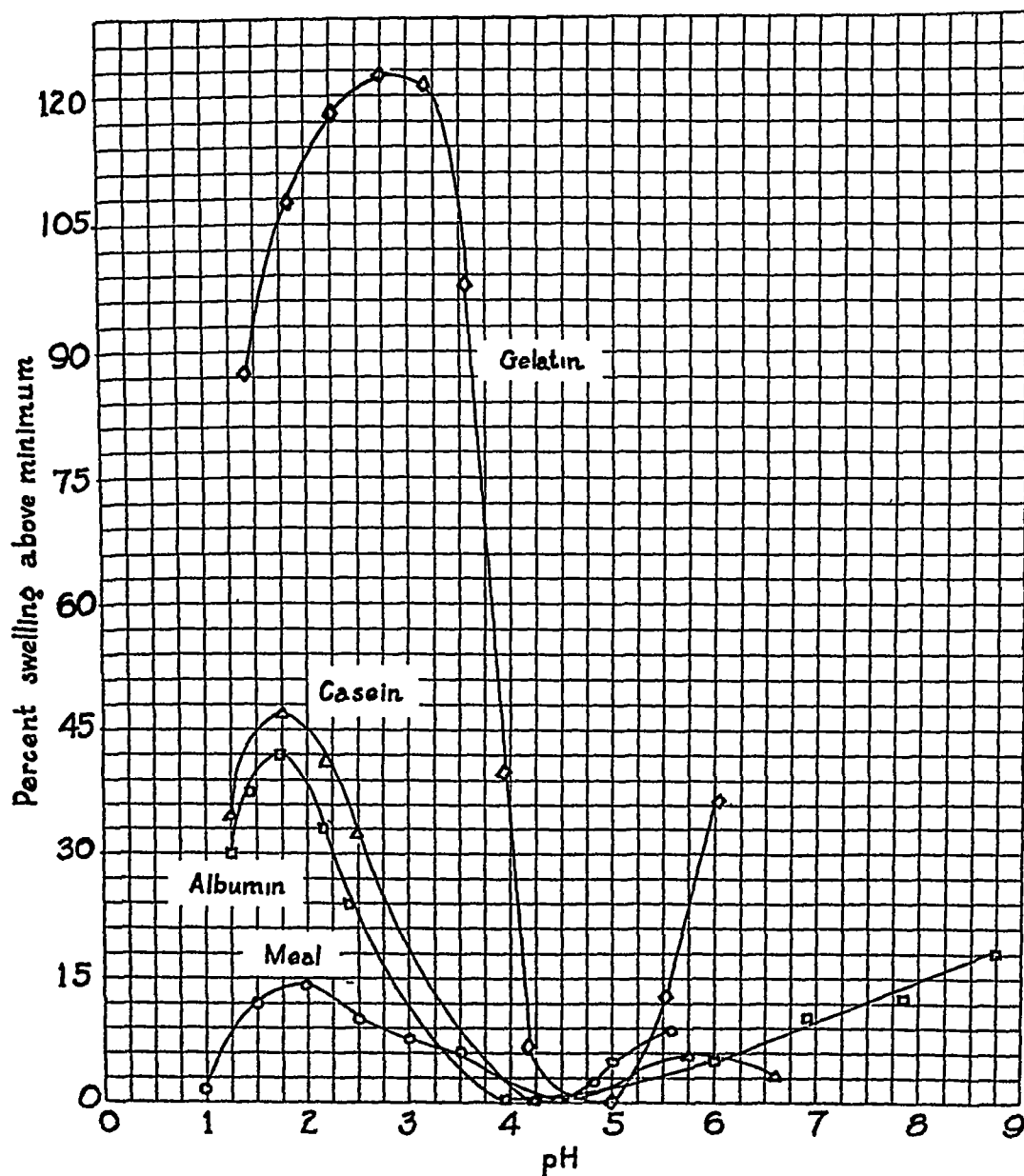


FIG 4 The per cent swelling above minimum volume of different foods at different pH values brought about by addition of acid or alkali

bactericidal effect. Somewhat similar findings were obtained with a strain of *Staphylococcus aureus* and also with a non-pigmented staphylococcus, although these organisms were apparently a little more sensitive to acid. Certainly any acid replacement therapy in achlorhydria would not lower the pH of a meal sufficiently to have effective bactericidal action as far as these

TABLE II
The Effect of pH of Meal on Destruction of Bacteria

Non-pigmented Ahemolytic Staph		Staph aureus		E coli		Beta streptococcus	
pH	Growth	pH	Growth	pH	Growth	pH	Growth
5.6	++++	5.7	++++	5.5	++++	5.8	++++
5.0	++++	5.3	++++	4.9	++++	5.0	++++
4.0	++++	4.6	++++	4.5	++++	4.5	+++
3.4	++++	3.9	+++	4.0	+++	4.0	±
3.0	++++	3.5	+++	3.6	+++	3.5	0
2.5	++++	2.9	+++	3.0	+++	3.0	0
2.0	+	2.6	+	2.4	+++	2.5	0
1.5	+	1.9	0	2.0	+++	1.9	0
1.1	±	1.5	+	1.4	0	1.4	0

organisms are concerned. On the other hand, certain organisms, and probably these include some of the more pathogenic bacteria such as the strain of beta streptococcus shown in table 2, are definitely destroyed under these conditions at pH values below 4.5. Such effective values could be reached with four to six 420 mg capsules of glutamic acid hydrochloride or about 60 c.c. of normal citric acid or lemon juice. In all probability certain pathogenic spores or encapsulated organisms could tolerate extremely low pH values.

The Effect of pH on Calcium Solution On an adequate dietary calcium intake (0.7 gm) the greater part of the calcium is furnished by milk and is consequently bound to protein. Van Slyke and Baker¹⁴ showed that the calcium was liberated from casein by acid addition and that this solution increased up to the isoelectric point of casein (pH 4.7) when all calcium was freed. Holt, La Mer and Chown¹⁵ have shown that as the various calcium phosphates are acidified, complete solution takes place below pH 5.0. Ivy and associates⁴ have shown that stomach acid is essential for normal bone structure, at least in the growing animal.

That in the solution of calcium salts a time factor exists has frequently been appreciated and was again emphasized by Holt and coworkers for the calcium phosphate systems. We have checked the splitting of calcium from casein at different pH levels under conditions as found in the stomach. Ten c.c. milk were curdled with renin at 37.5° C for 30 minutes. Acid was then added to obtain the desired pH values, the volume was diluted to 15 c.c., and incubation continued with gentle shaking for another three hours. The mixtures were filtered to obtain the soluble calcium, the filtrates were all brought to pH 7.0, and the phosphates were removed with ferric chloride and calcium determined according to the method of Hoffman¹⁶.

Figure 5 shows the soluble calcium split from milk curd at various pH values obtained by hydrochloric and citric acid additions at the end of a three hour agitation at 37.5° C. The importance of adequate lowering of the pH of the gastric contents for calcium liberation can readily be seen. Under

these conditions there was little if any difference between the effect of hydrochloric or citric acid at any given pH. It will be noted, however, that under conditions of complete equilibrium (Loeb, Van Slyke et al), all calcium should be liberated at pH 4.7, the isoelectric point of casein. This was not the case, however, for a three hour period of incubation (the average emptying time of the stomach), for calcium liberation was found to be moderately slow but was increased by lowering the pH. In conditions of rapid emptying time of the stomach the amount of calcium liberated is proportionately decreased.

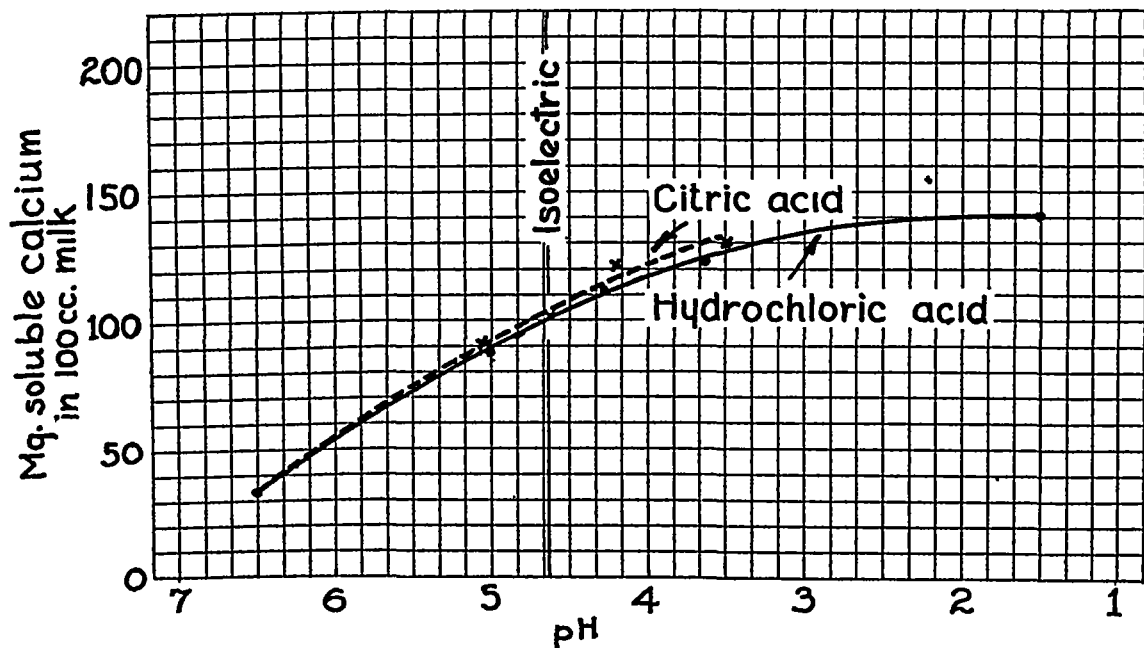


FIG 5 The solubility of calcium from curdled milk at various pH values in three hours at 37.5° C

The Effect of Anacidity on Thiamine Stability Since thiamine is destroyed in alkaline solution exposed to oxygen and stability is promoted on the acid side, the question of destruction of thiamine in anacidity has been raised. The work of Melnick, Robinson and Field,¹⁷ however, has shown that thiamine is stable in normal gastric juice from pH 1.5 to 8.0 during a 16 hour incubation at 37.5° C.

The Probable Amount of Acid Secretion in the Stomach Since the amount of hydrochloric acid secreted by the stomach for a meal must be enough to bring the pH value to about 1.8 or lower, this amount should be approximately comparable to the 104 c.c. normal hydrochloric acid that was required to bring the pH of an average meal to this pH in our experiments. The average meal would accordingly require about 3.8 gm hydrochloric acid. The actual amount, however, must be considerably more, for digested protein has an increased buffer capacity, gastric mucin has an additional buffer value, and alkaline regurgitation from the intestines (said to be a normal process¹⁸) would result in partial neutralization. The lower values

usually considered normal for acid secretion are based on inadequate test meals (toast and tea) and consequently on only partial stimulation of acid secretion. From a practical standpoint, the effect of food on gastric acidity is a summation effect of the acid stimulating and acid neutralizing abilities of the various dietary constituents as well as the emptying rate of the stomach.

CONCLUSIONS AND SUMMARY

1 The addition of acid to a representative ground meal at body temperature in vitro shows that the usual amount of acid used in replacement therapy has but little relative effect on the pH of the meal, because of the buffer value of the food. The amount of any acid necessary to bring the pH of a meal to the normal physiological post-meal range (pH 1.6 to 1.8) or for peptic activation (below pH 2.0) is of such magnitude that practical aspects preclude its administration. For USP hydrochloric acid this amount would be 35 cc. Even twenty 420 mg capsules of glutamic acid hydrochloride with a meal would fail to produce normal acidity or activate pepsin.

2 Upon acid addition, different foods have a buffer or neutralizing effect approximately proportional to their protein content. For this reason an average large meal may have from 15 to 20 times the neutralizing ability of the usual Ewald test meal of 3 gm protein. Consequently the evaluation of acid replacement therapy with an Ewald meal may give altogether erroneous results.

3 Except for gelatin, the swelling of proteins as a step in solution and digestion is not appreciably influenced by even the largest doses of acid advocated in replacement therapy. In fact, the usual doses of acid advocated bring the pH of a meal to the range of minimum swelling of the proteins.

4 Usual acid replacement therapy does not bring the pH sufficiently low to have any appreciable bactericidal effect. Certain strains of staphylococci and coli are uninfluenced by exposure in a meal to the maximum amount of acid therapy practical. In fact, only complete attainment of the normal post-meal gastric pH gives anywhere nearly complete bactericidal action, and even this pH may not be effective within the normal emptying time of the stomach for certain acid-resistant, encapsulated or sporulated organisms. On the other hand, certain types of pathogenic organisms are very sensitive to even slight lowering of the pH below neutrality and acid therapy might well be a factor in their destruction.

5 Decreasing pH values from 6.5 to 1.5 are instrumental in proportionally increased liberation of calcium from milk over a three hour period. On the basis of complete equilibrium, maximum calcium liberation should occur at the isoelectric point of casein, pH 4.7, but during a three hour period of incubation complete equilibrium has not been obtained and further lowering of the pH results in more rapid liberation of calcium.

6 Anacidity or hyperacidity has no effect on thiamine destruction.

7 The amount of hydrochloric acid secreted by the stomach for an average meal must be in excess of 104 c c normal, 35 c c U S P , or 3.8 gm as calculated from our data

REFERENCES

- 1 BENNETT, T I, and RYLE, J A Studies in gastric secretion V A study of normal gastric function based on the investigation of one hundred healthy men by means of the fractional method of gastric analysis, *Guy's Hosp Rep*, Series 4, 1921, 1, 286
- 2 VANZANT, F R, ALVAREZ, W G, EUSTERMAN, G B, DUNN, H L, and BERKSON, J The normal range of gastric acidity from youth to old age an analysis of 3746 records, *Arch Int Med*, 1932, xlix, 345
- 3 RUFFIN, J M, and DICK, M The significance of gastric acidity after histamine stimulation a statistical study of 2877 gastric analyses, *ANN INT MED*, 1939, xii, 1940
- 4 BUSSABARGER, R A, FREEMAN, S, and IVY, A C The experimental production of severe homogenous osteoporosis by gastrectomy in puppies, *Am Jr Physiol*, 1938, cxxi, 137
- 5 CROHN, B B Studies in fractional estimation of stomach contents, III Effects of hydrochloric acid therapy on the acid titer of the stomach during digestion, *Am Jr Med Sci*, 1918, clvi, 656
- 6 KERN, R A, ROSE, E, and AUSTIN, J H Effect of orally administered hydrochloric acid upon gastric contents in normal individuals and in patients with achlorhydria, *Jr Clin Invest*, 1926, ii, 545
- 7 STAPHNE, E C The effect of therapeutic doses of dilute hydrochloric acid on the teeth, *Proc Staff Meet Mayo Clin*, 1933, viii, 157
- 8 SHAY, H, and GERSHON-COHEN, J A comparison of the effectiveness of glutamic acid hydrochloride and dilute hydrochloric acid as the replacement therapy in an acidity measured by fractional gastric acid titration and hydrogen-ion concentration curves, *ANN INT MED*, 1935-1936, ix, 1628
- 9 SANSUM, W D, and GRAY, P A Achlorhydria gastrica A simple management, *California and West Med*, 1929, xxx, 221
- 10 SHOHL, ALFRED T, and KING, JOHN H Determination of the acidity of gastric contents II The colorimetric determination of free hydrochloric acid, *Bull Johns Hopkins Hosp*, 1920, xxxi, 158-162
- 11 HAGGARD, H W, and GREENBERG, L A The influence of certain fruit juices on gastric function, *Am Jr Digest Dis*, 1941, viii, 163
- 12 NORTHROP, J H The effect of various acids on the digestion of protein by pepsin, *Jr Gen Physiol*, 1919, i, 607
- 13 LOEB, J Proteins and the theory of colloidal behavior, 1922, McGraw-Hill Book Company, New York, p 78
- 14 VAN SLYKE, L I, and BAKER, J C The preparation of pure casein, *Jr Biol Chem*, 1918, xxi, 127
- 15 HOLT, L E JR, LA MER, V K, and CHOWN, II B Studies in calcification I The solubility product of secondary and tertiary calcium phosphate under various conditions, *Jr Biol Chem*, 1925, lxi, 509
- 16 HOFFMAN, W S The micro determination of fixed bases, calcium and sulfates in urine, *Jr Biol Chem*, 1931, xciii, 787
- 17 MERICI, D, ROBINSON, W D, and FIRD, H Fate of thiamine in the digestive secretions, *Jr Biol Chem*, 1941, cxxviii, 49
- 18 SPENCER WILLIAM H MEYER, GEORGE P, REHFUSS, MARTIN E, and HAWK, PHILIP B Gastro-intestinal studies XII Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach, *Am Jr Physiol*, 1916, xxix, 459-470

A METHOD FOR THE CONTINUOUS RECORDING OF GASTRIC pH IN SITU. IV. FURTHER EVALUATION OF THE EFFICACY OF ANTACIDS IN VITRO AND IN THE HUMAN BEING *

By N E ROSSETT, M D , and JAMES FLEXNER, M D ,
New York, N Y

A method for the continuous recording of gastric pH in situ was recently described^{1,2} and utilized in providing continuous pH recordings in vivo (dogs) and in vitro. Sodium bicarbonate, Sippy A powders, magnesium trisilicate, magnesium superoxol, and aluminum hydroxide were tested.³ The present communication deals with titrations in vitro and in the human stomach of these and other antacids commonly used in ulcer therapy.

MATERIALS AND METHODS

In Vitro Thirty c c of 0.1 normal hydrochloric acid and 70 c c of distilled water were placed in a beaker to represent the fasting contents (pH 1.4) of a hyperchlorhydric human stomach. This solution was led by rubber tubing to a glass electrode connected to a continuous pH recorder. A pumping system previously described² was used to maintain circulation of the mixture around the glass electrode. After a 10 minute control period the antacid, made up to 100 c c with distilled water, was permitted to flow over the glass electrode which was then washed by 50 c c of distilled water. One tenth normal hydrochloric acid was added to the beaker at the rate of 120 c c per hour which simulates the secretory rate of the hyperchlorhydric stomach.

In Vivo Patients on the Second (Cornell) Medical Division, Bellevue Hospital, were chosen as subjects. The fasting subject was seated in a wheel chair with the back sloping 60 degrees. The purpose and safety of the procedure were explained, after which the soft palate and pharynx were anesthetized by the application of a 2.0 per cent pontocaine solution containing one part in 20,000 adrenalin hydrochloride. Five minutes after the application of pontocaine the stomach tube was passed to a distance of 18.5 inches from the incisor teeth, at which level it was kept throughout the experiment. The stomach tube used is illustrated in figure 1. Its lumen contains a small glass electrode with its shielded lead, a potassium chloride reference electrode tube, and reserve space to permit the passage of fluids. The location of the tube tip on the greater curvature just above the antrum was verified fluoroscopically. The subject's stomach was emptied. After determining

* Received for publication October 6, 1941.

From the Second (Cornell) Medical Division, Bellevue Hospital, and the Department of Medicine, Cornell Medical College.

the amount and pH of the fasting contents, a measured quantity was returned to the stomach and the recorder started. When the same subject was used to evaluate several antacids the same quantity was used in each experiment. After a short control period the antacid was added in the manner described for the beaker experiments. On several occasions, because of rapid emptying, additional distilled water had to be added before completion of an experiment in order to keep the glass electrode in a fluid medium. At the end of an experiment the stomach was emptied,

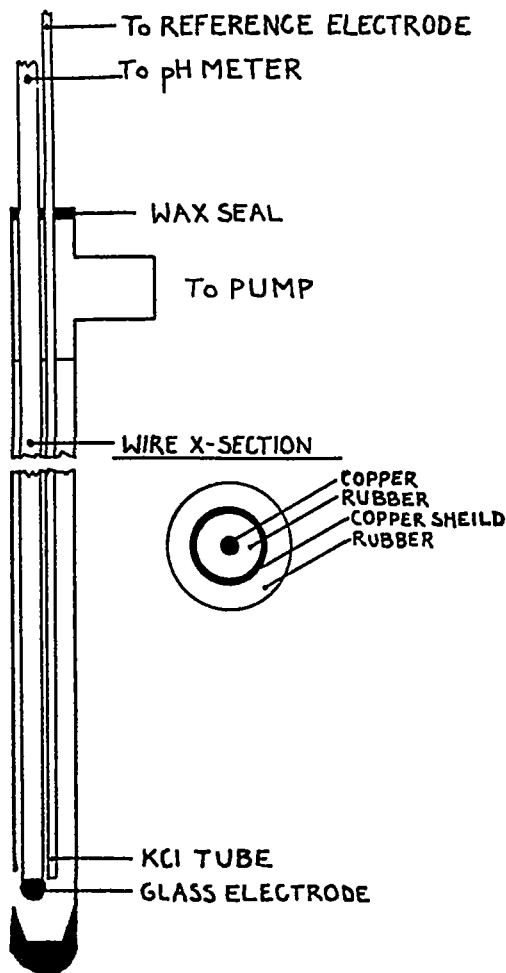


FIG 1 Stomach tube

contents mixed, and pH determined with the standard glass electrode. Several recordings also were made using a continuous flow glass electrode to which gastric contents were led by nasal tube.

RESULTS

Figure 2 was made by superimposing the titration curves of the indicated antacids. One gram quantities were used so that the tracings would be comparable. Inspection reveals that calcium carbonate causes the most marked and prolonged rise in pH. In order of decreasing effect the re-

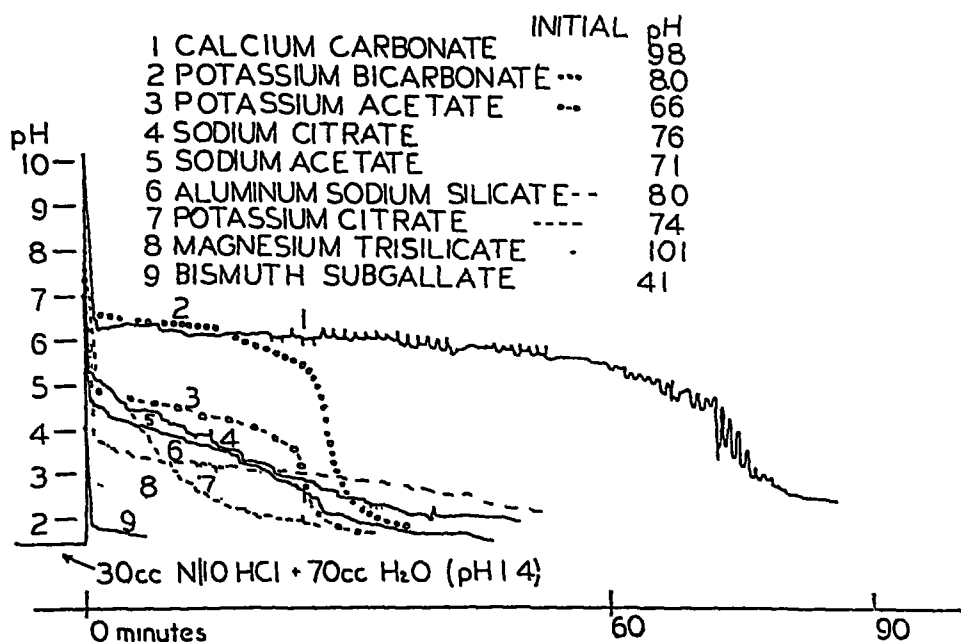


FIG 2 In vitro

maining antacids are potassium bicarbonate, potassium acetate, sodium citrate, sodium acetate, aluminum sodium silicate, potassium citrate, magnesium trisilicate, and bismuth subgallate. Tracings for bismuth subnitrate and bismuth subcarbonate (initial pH 3.9 and 7.0 respectively) were omitted because they were almost identical with the tracing for bismuth subgallate.

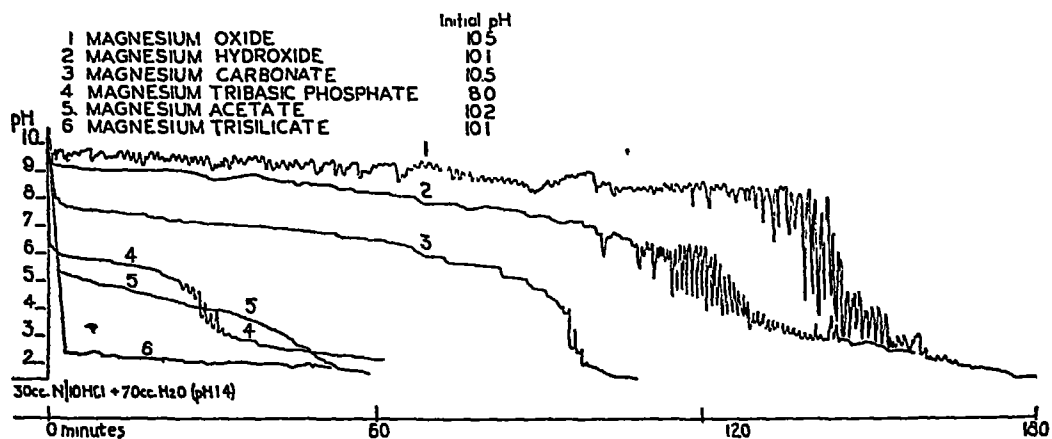


FIG 3 In vitro

In figure 3 the titration curves show the pH changes after the addition of 10 gram quantities of magnesium compounds. The marked rise in pH caused by magnesium oxide is readily demonstrated. A tracing for magnesium peroxide (initial pH 10.7) was omitted because this followed closely the curve for magnesium hydroxide. In figure 4 curves secured with mix-

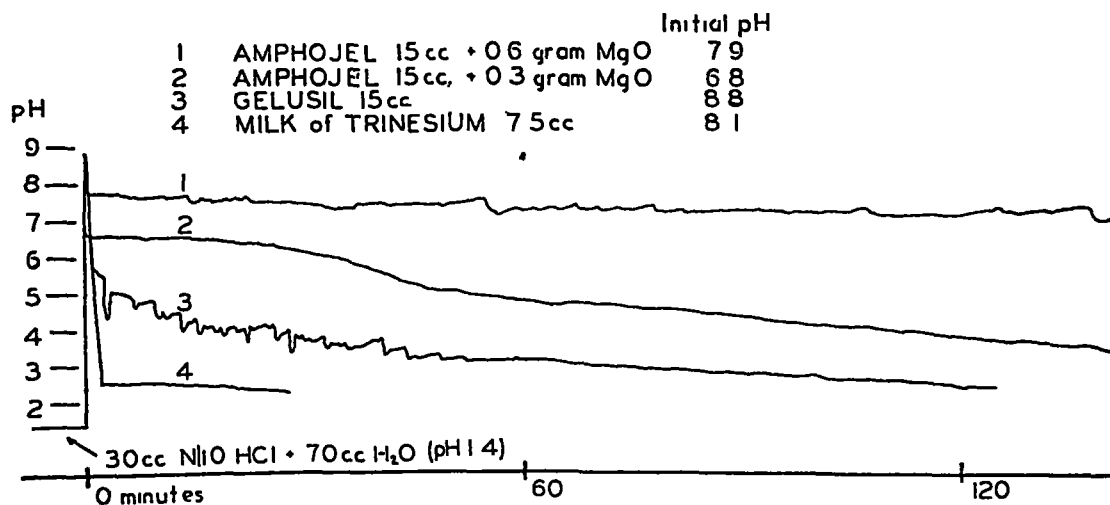


FIG. 4 In vitro

tures of aluminum hydroxide and magnesium trisilicate (Gelusil and Milk of Trinesium) are shown together with that obtained with a more rational mixture, aluminum hydroxide (Amphojel) and magnesium oxide. Figure 5 presents the titration curves for a glass of sweet milk (200 c c) and sweet

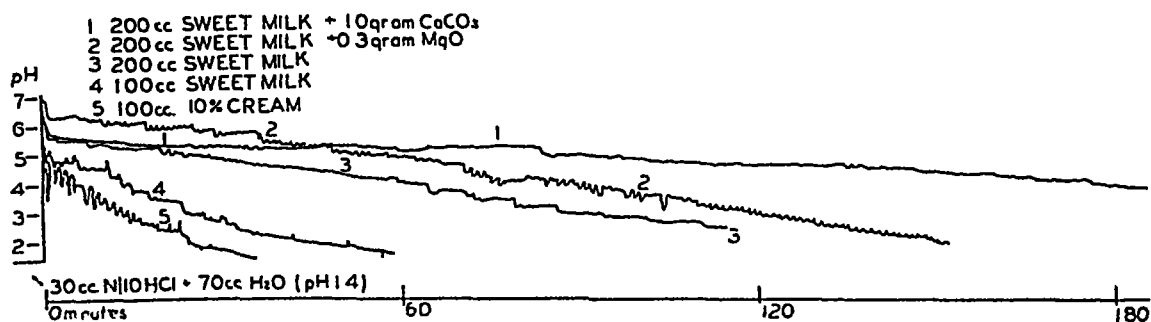


FIG. 5 In vitro

milk to which calcium carbonate and magnesium oxide have been added. It will be noted that there is an additive effect which produces a long acting antacid and that the high initial pH of calcium carbonate or magnesium oxide alone does not appear, having been effectively buffered by the milk. The tracings for 100 c c of sweet milk and 100 c c of 10 per cent cream illustrate the better buffering action of the sweet milk. Inspection of the human recordings reveals that the pH changes follow closely the in vitro results. The tracings shown were selected from a total of 66 experiments on 40 subjects.

The subject for figure 6 was T. K., a 40-year-old white male, whose diagnosis was exogenous obesity. He denied any gastrointestinal complaints. In this case histamine 0.1 mg. per kilogram was used five minutes after the start of each experiment. The two experiments recorded, as in all the in vivo experiments, were done on successive days. It will be noted that al-

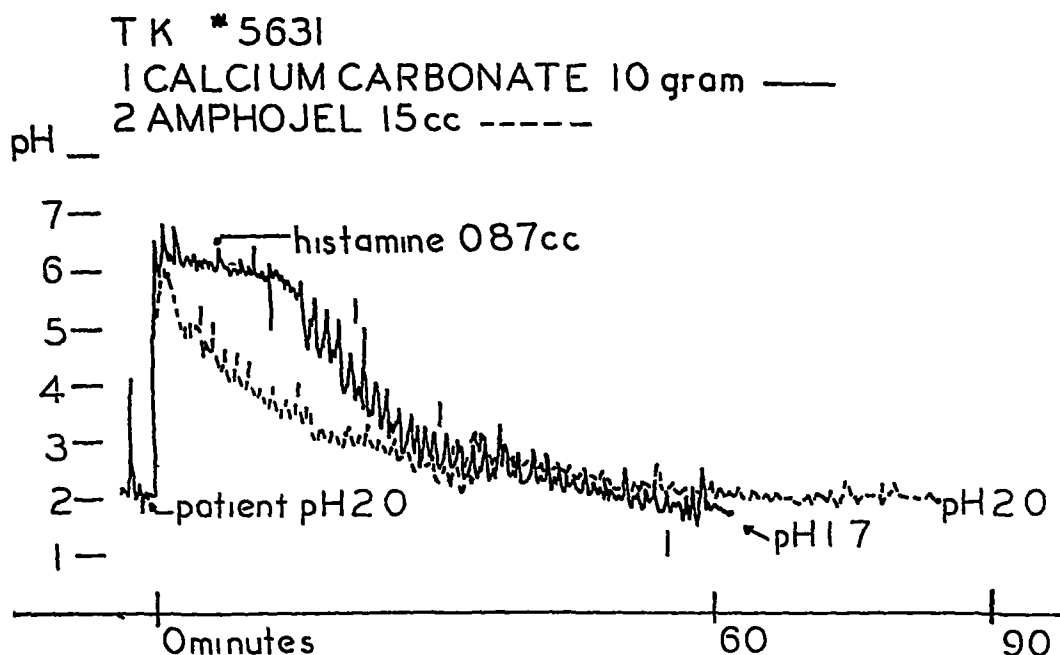


FIG 6

though calcium carbonate gives a higher initial pH than an equivalent quantity of aluminum hydroxide in its liquid form (15 cc Amphojel, approximately a 6 per cent suspension), the latter has a more sustained action

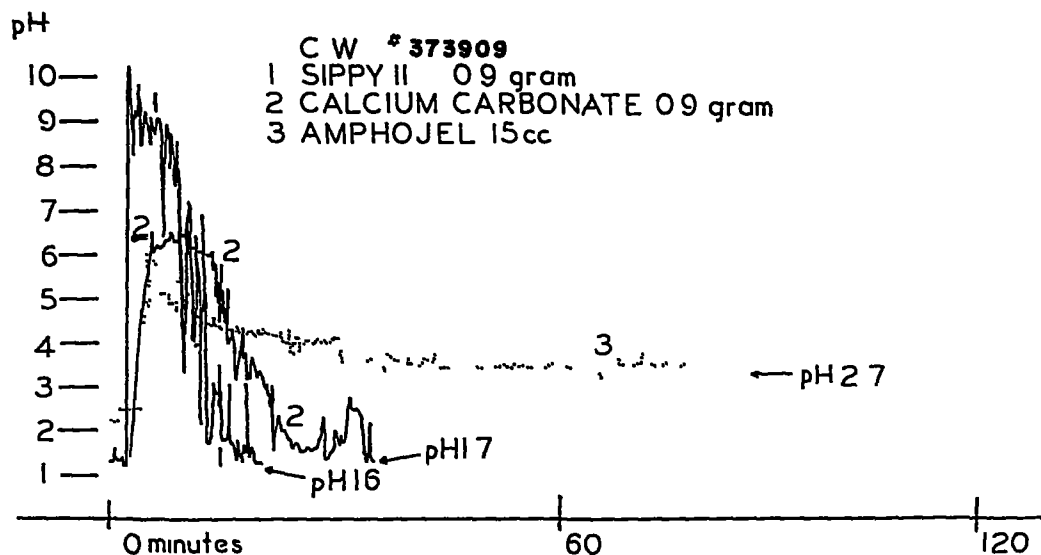
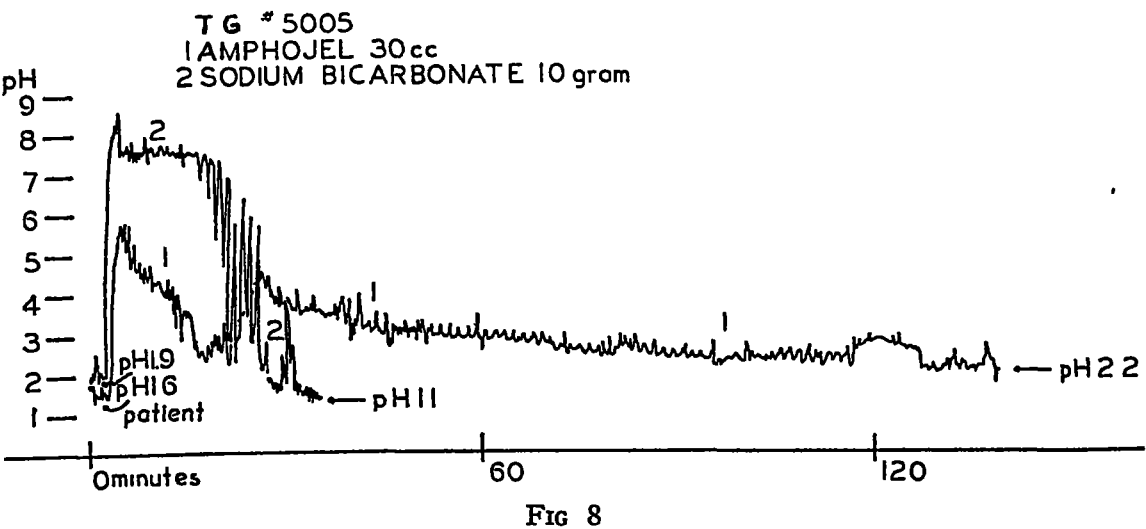


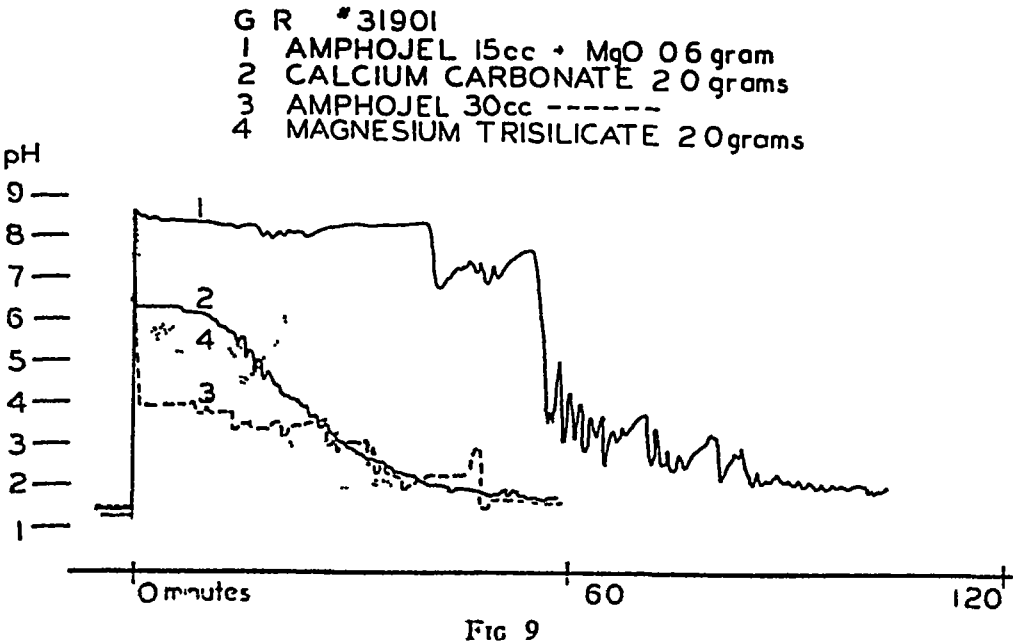
FIG 7

C W, the subject for figure 7, was a 51-year-old white male who had a roentgenological diagnosis of duodenal ulcer. His tracings demonstrate the very high but transient rise of pH in response to 0.9 gm Sippy II powder (magnesium oxide and sodium bicarbonate in equal quantities). The re-



sults with calcium carbonate and Amphojel were in the same order as in patient T K

In figure 8 the tracings for T G , a 35-year-old white male who was admitted because of hemorrhage from a gastric ulcer, are shown. They illustrate the high pH achieved with sodium bicarbonate, the rapid exhaustion of its buffering action, and probably the rebound phenomenon (pH 10 to 11) as contrasted with the sustained action of aluminum hydroxide



The tracings for G R , a 39-year-old negress (figure 9) with roentgenological evidence of a duodenal ulcer, are illustrative of the prolonged anti-acid effect of an aluminum hydroxide-magnesium oxide mixture and the reduction of the high pH of magnesium oxide by the buffering action of aluminum hydroxide in such a mixture

DISCUSSION

The response to environmental ^{4, 5, 6, 7} factors by different patients becomes relatively constant when each patient is tested repeatedly under the same experimental conditions. Thus, the response of each patient to various antacids is in the same relative order even though there may be a marked absolute variation in the effect of these antacids in different individuals as determined by secretory rate, nature of secretion, emptying time and regurgitation. Our findings in the human being support the previous report ⁸ that in vitro experiments with the recording glass electrode afford an easy and satisfactory method of obtaining information regarding the antacid properties of various substances.

In addition to the extent of rise in pH and its duration, other factors must be considered in evaluating the efficacy of an antacid. That the human stomach is not normally subjected to high pH values is evident from the work of Bridges and Mattice ⁸ which showed that over 70 per cent of 2000 representative foods had a pH between 5 and 7. Only three foods had a pH over 8. These findings suggest 7 as the upper limit of the desirable pH range. A rise to 7 or above removes the acid medium which may be necessary to protect the gastric mucosa from the strong proteolytic action of regurgitated trypsin and erepsin which are active in alkaline media. Most investigators feel that the lower effective pH limit is between 5, at which point pepsin is practically inactive, and 3.5, a level at which peptic activity is greatly diminished. Probably more important than peptic activity is the pH level at which pylorospasm is relieved and the vicious circle of pylorospasm, hypersecretion, hypermotility, and ischemia is broken. From the duration of the clinical response this relief may still be present at a pH of 2.5 and a rise above 4.5 never seems to be necessary. The pH rise from a fasting level of 1.5 to a buffered level of 2.5 constitutes an actual reduction to one tenth of the initial hydrogen ion concentration.

Presumably pepsin inactivation is desirable. Mutch ⁹ has reported its absorption by synthetic magnesium trisilicate and Komerov and Komerov ¹⁰ and Schiffrin and Komerov ¹¹ demonstrated the precipitation and inactivation of pepsin in vitro and in vivo in dogs by colloidal aluminum hydroxide. With both substances more complete removal of pepsin was obtained if the free hydrochloric acid was buffered, but adequate pepsin inactivation was obtained without excessive reduction of acidity with aluminum hydroxide.

It is also essential that the antacid does not permanently remove the acidifying effect of gastric contents or the latter will not be available to counteract the alkalinity of the digestive juices present in the small intestine. For example, calcium carbonate (and all antacids which are not amphoteric in nature) yields neutral salts which cannot react with the alkaline intestinal juices, permits the intestinal alkalis to be reabsorbed, and taxes the buffer mechanism of the blood. The absence of this undesirable effect permits

the use of as large a dose as is necessary of amphoteric buffers without danger of systemic alkalosis

CONCLUSIONS

1 Antacids commonly used in ulcer therapy have been evaluated by means of a continuous recording pH meter in vitro and in the human being

2 The similarity of experiments in vitro and in the human stomach recommend the former method as an adequate procedure for analysis of pH changes by various antacids

3 Magnesium oxide, peroxide, hydroxide, and carbonate are the most effective antacids in a purely chemical sense

4 These as well as calcium carbonate when combined with milk or colloidal aluminum hydroxide are effectively buffered in their alkaline range and produce long acting antacids

5 Milk or aluminum hydroxide in adequate dosage best fulfills the physiological criteria of ideal antacids as stated in our discussion

REFERENCES

- 1 FLEXNER, J, KNIAZUK, M, and NYBOER, J Method for continuous recording of gastric pH in situ, *Science*, 1939, **xc**, 239
- 2 FLEXNER, J, and KNIAZUK, M A method for the continuous recording of gastric pH in situ II Experimental details, *Am Jr Digest Dis*, 1940, **xii**, 138
- 3 FLEXNER, J, and KNIAZUK, M A method for the continuous recording of gastric pH in situ III Evaluation of the efficacy of certain antacids, *Am Jr Digest Dis*, 1941, **xiii**, 45
- 4 VAN LIRE, E J, and SLFETH, C K The emptying time of the normal human stomach as influenced by acid and alkali, *Am Jr Digest Dis*, 1940, **xii**, 118
- 5 BROOMFIELD, A L, CHEN, C K, and FRENCH, L R Basal gastric secretion as a clinical test of gastric function with special reference to peptic ulcer, *Jr Clin Invest*, 1940, **xix**, 863
- 6 GARLIN, C, ET AL Secretion gastrique provoquee par simple presence d'une sonde d'Einhorn dans les voies digestives, *Bull et mem Soc med d hôp de Paris*, 1929, **liii**, 984
- 7 HARDY, H H, and QUANSTRON, V E Effect of gastric distension on gastric secretion, *Proc. Soc Exper Biol and Med*, 1937, **xxxvii**, 28
- 8 BRIDGES, M A, and MATTICI, M R Over 2000 estimations of the pH of representative foods, *Am Jr Digest Dis*, 1939, **xii**, 440
- 9 MITCH, N Synthetic magnesium trisilicate Its action in the alimentary tract, *Brit Med Jr*, 1936, **i**, 205
- 10 KOMEROV, S A, and KOMEROV, OIGA The precipitability of pepsin by colloidal aluminum hydroxide, *Am Jr Digest Dis*, 1940, **xii**, 66
- 11 SCHIFFEIN M J, and KOMEROV, S A The inactivation of pepsin by compounds of aluminum and magnesium, *Am Jr Digest Dis*, 1941, **xiii**, 215

SULFONAMIDE THERAPY OF BACTERIAL ENDOCARDITIS; RESULTS IN 42 CASES *

By W R GALBREATH, M D, and EDGAR HULL, M D, F A C P,
New Orleans, Louisiana

DURING the years 1938 to 1941, inclusive, there were 67 cases of bacterial endocarditis among the patients admitted to the Charity Hospital. Forty-two of these cases received therapy with one or more of the sulfonamide drugs. This report, reviewing the 42 cases which received sulfonamide therapy, is made in order to add data to those recorded by numerous authors relating to the effectiveness of the sulfonamide drugs in bacterial endocarditis.

Criteria for Diagnosis The diagnosis was based either upon (1) a compatible clinical picture plus one or more positive blood cultures, or (2) necropsy evidences. In 32 cases the diagnosis was established ante mortem by the first criterion, in the other 10 cases the presumptive diagnosis of bacterial endocarditis, unestablished during life of the patients by blood culture, was confirmed by postmortem examination. No attempt has been made to differentiate between acute and subacute forms of the disease.

Data Regarding Incidence The cases were evenly distributed between the sexes and races, there being 12 white males, 10 white females, nine colored males, and 11 colored females. The age range was from two to 75 years, the majority of cases falling between the ages of 15 and 30. The duration of hospital stay varied from two to 202 days, the average stay being about seven weeks.

Sites of Vegetations Based on postmortem findings in 30 cases, and on clinical data in 12 cases, the sites of vegetations may be listed as follows:

Mitral valve	18 cases
Aortic valve	8 cases
Mitral and aortic valves	7 cases
Tricuspid valve	2 cases
Aortic and tricuspid valves	1 case
Pulmonary valve	1 case
Aortic, mitral, and tricuspid valves	1 case
Congenital defects	4 cases

Bacteriology In the 32 cases with positive blood cultures, the following organisms were recovered:

<i>Streptococcus viridans</i>	20 cases
Beta hemolytic streptococcus	1 case
<i>Staphylococcus aureus</i>	4 cases
<i>Staphylococcus albus</i>	2 cases
Pneumococcus	3 cases
<i>Streptococcus viridans</i> and pneumococcus	1 case
<i>Eberthella typhi</i>	1 case

In 10 cases positive blood cultures were not obtained.

* Received for publication February 6, 1942.

From the Departments of Medicine of the Louisiana State University School of Medicine and the Charity Hospital of Louisiana in New Orleans.

Therapy Sulfanilamide alone was employed in 20 cases, sulfanilamide and sulfapyridine in nine cases, sulfapyridine alone in six cases, sulfapyridine and sulfathiazole in three cases, sulfamethylthiazole in one case, sulfanilamide, sulfapyridine, and sulfathiazole in two cases, and sulfapyridine, sulfathiazole, and sulfadiazine in one case

There was great variation in the total amounts of sulfonamide drugs given to different patients, but as a rule the dosage per day was large. The total amounts given to individual patients bore a direct relationship to the duration of the hospital stay. Thus the largest total dose, 1043 grams, was given to a patient who spent 202 days in the hospital, and the smallest total dose, two grams, was given to a patient whose hospital stay was but two days. In most cases sulfonamide therapy was continued until death, or until toxic effects of the drugs used necessitated their discontinuance. The successive use of different drugs of the sulfonamide groups in a given patient was always due to failure of the drug used first, or to the occurrence of toxic manifestations due to the first drug used.

Frequent blood transfusions were given to most of the patients. In two patients hyperpyrexia induced by the intravenous injection of typhoid vaccine was used as an adjunct to sulfonamide therapy. Treatment was otherwise supportive and symptomatic.

Results All of the patients died. In some patients there were temporary remissions in the temperature curve, but for the most part the disease pursued a course apparently unaffected by the treatment.

Necropsy Findings Autopsy was performed in 30 cases, 71 per cent of the total number. In all these cases characteristic lesions of acute or subacute vegetative endocarditis were found. In no case was there evidence of healing of the lesions. Evidence of embolism was present in 28 cases. The kidneys and spleen were the most frequent sites of infarction, but, in the order of their frequency, infarcts of the brain, lungs, heart, liver, and thyroid were also encountered.

COMMENT

Nothing is proved by this series of cases regarding the efficacy of the sulfonamide drugs in the treatment of bacterial endocarditis. There is only proof that in these cases the drugs used, in the dosage employed and in the duration of their employment, were without curative effect. It is to be noted that sulfanilamide alone was used in almost half the cases, sulfapyridine, alone or in combination with other drugs, in 21 cases, exactly half of the series; sulfathiazole in only six cases, and sulfadiazine in but one. It should also be noted that this series is unusual in that almost half of the cases were due to organisms other than the *Streptococcus viridans*.

This series, therefore, adds only to the total number of reported cases of bacterial endocarditis in which sulfonamide drugs have been used. Since the cases herein reported are taken from a total number of 67 proved cases

of bacterial endocarditis encountered during a four-year period, additional data regarding the outcome in cases which have not been treated with sulfonamide drugs are furnished by this report. There were 25 such cases observed during the four-year period, and 25 deaths.

SUMMARY

During the four-year period covering the years 1938 to 1941, inclusive, 67 proved cases of bacterial endocarditis were encountered in the Charity Hospital. One or more of the sulfonamide drugs were used in the treatment of 42 cases, and no sulfonamide drugs in 25. All 67 of the patients died.

CLINICAL EVALUATION OF CEDILANID *

By MAURICE SOKOLOW, M D , and FRANCIS L CHAMBERLAIN, M D ,
San Francisco, California

THE pure glycosides of digitalis have been the subject of many recent pharmacological and clinical investigations. Originally all the studies were purely chemical, but they have assumed clinical importance. The crude whole leaf of *Digitalis purpurea* commonly used in clinical medicine has never been an ideal therapeutic agent. The various preparations differ widely in composition and potency, and require biological standardization. Furthermore, the U S P. product may vary in strength with each revision. For instance, the digitalis in U S P XI is approximately 30 per cent more potent than that in U S P X, and the United States Pharmacopeia allows a 40 per cent range between the weakest and the strongest preparation. Gold ¹ assayed various commercial products and found a three-fold difference in strength although all were labeled U S P XI. This difference in strength is of great importance when parenteral therapy of digitalis in gravely ill patients is considered or when constant potency is desired for maintenance doses.

Smith ² and Stoll ³ were the pioneers in the chemical isolation of the pure glycosides of digitalis. Stoll studied both *Digitalis purpurea* and *Digitalis lanata*. A diagram from his monograph illustrates the similarities of, and the differences between the two types of digitalis (chart 1). Each has three glycosides but lanatoside C, the third glycoside of lanata, has no close chemical relationship to the glycosides of purpurea and is not found in the ordinary U S P *Digitalis purpurea*. This glycoside has been isolated in crystalline form and has been standardized by weight. It does not require biological assay.

Early clinical work has centered on lanatoside C because the pharmacologic observations of Moc and Visscher ⁴ suggested that it was the most potent and the least toxic of the glycosides. The earliest clinical reports which indicated that it was a potent therapeutic agent came from continental investigators. Wayne ⁵ specifically used digoxin, a breakdown product of lanatoside C, whereas others ^{6, 7} used lanatoside C. The first American reports were a series of articles by Gold and his co-workers on the pure glycosides ^{8, 9, 10}. The most extensive clinical study was made by Fahr and LaDue ¹¹ who showed that lanatoside C is potent both orally and intravenously and that the speed of action of the intravenous product resembles that of strophanthin. Our study of lanatoside C was begun independently two years

* Received for publication December 8, 1941

From the Department of Medicine, University of California Medical School, San Francisco

Aided by a grant from the Sandoz Chemical Works, Inc.

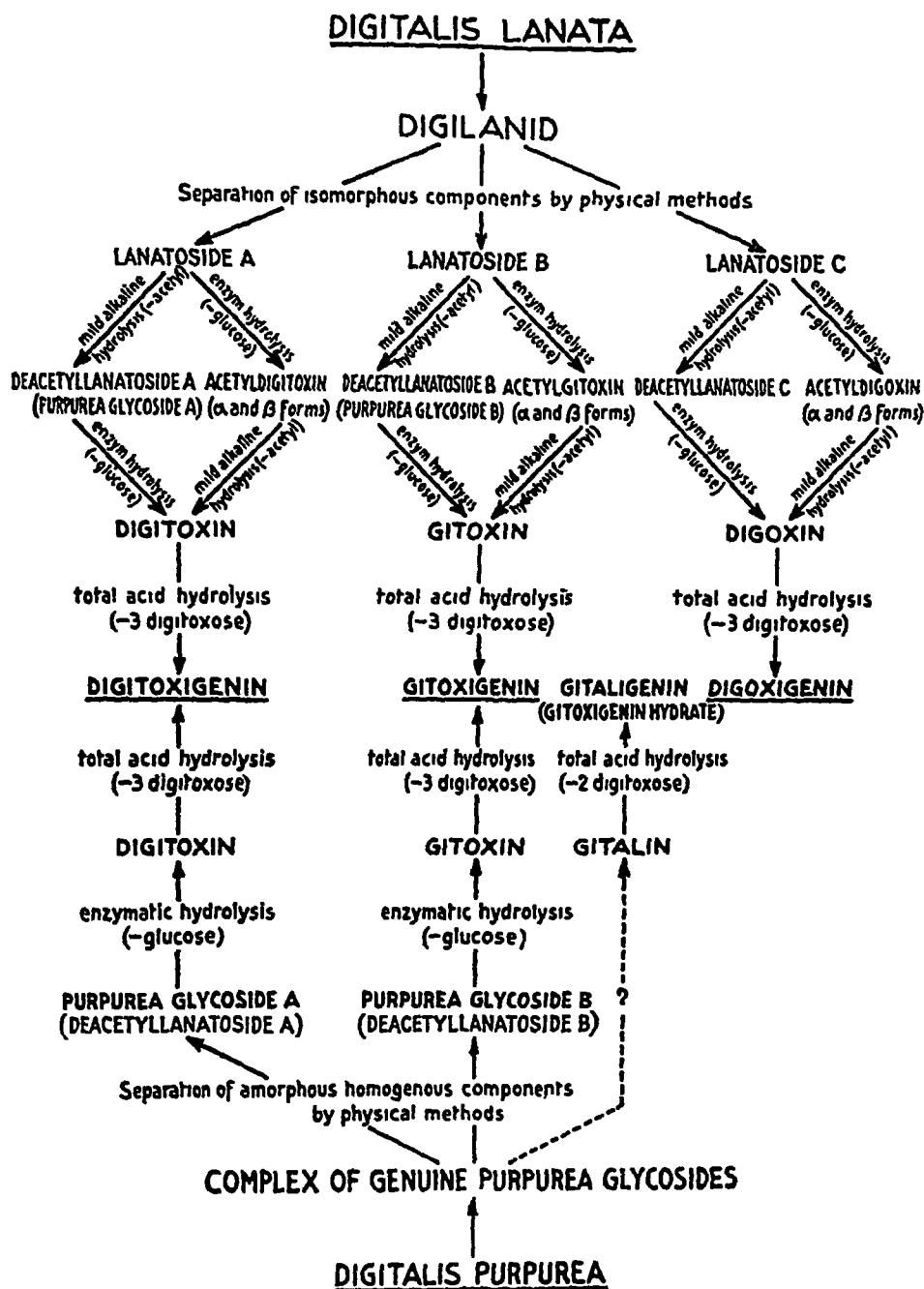


CHART 1 The newly discovered relationships between the lanata and purpurea glycosides (after Stoll and Kreis)

ago, and confirms and extends some of the observations made by Fahr and LaDue

In interpreting the dosage of lanatoside C, it is important to note, as was first emphasized by Gold,⁸ that dosage and toxicity of the pure crystalline glycosides cannot be deduced from comparative values obtained on test animals but must be determined clinically in man. The dosage must be con-

sidered in terms of milligrams and not of cat units. In man, one cat unit of digitalis leaf may produce the same clinical effects as five cat units of lanatoside C when both are given orally.

Lanatoside C (or Cedilanid) is marketed by the Sandoz Chemical Works, Incorporated. The oral preparation is made in tablets of 0.5 mg each and the intravenous preparation in ampoules, each cubic centimeter of which contains 0.20 mg of the drug. A cat unit is considered equivalent to 0.28 mg.

METHOD OF STUDY

The patients who were chosen for the investigation presented the usual indications for digitalis therapy, such as congestive failure, paroxysmal

Auricular Fibrillation ♀ cat 19 U12066

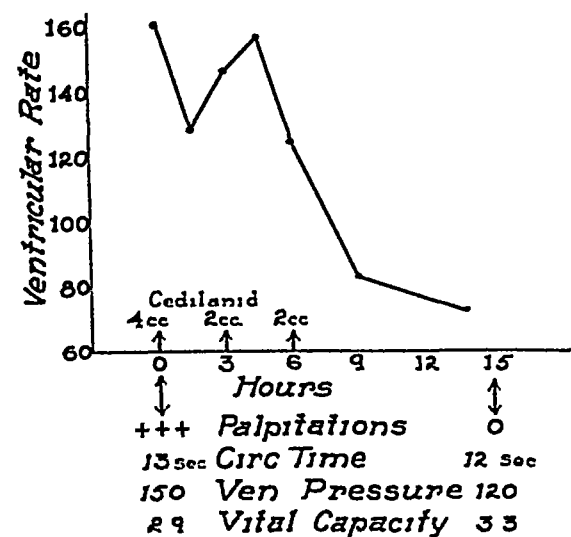


FIG 1

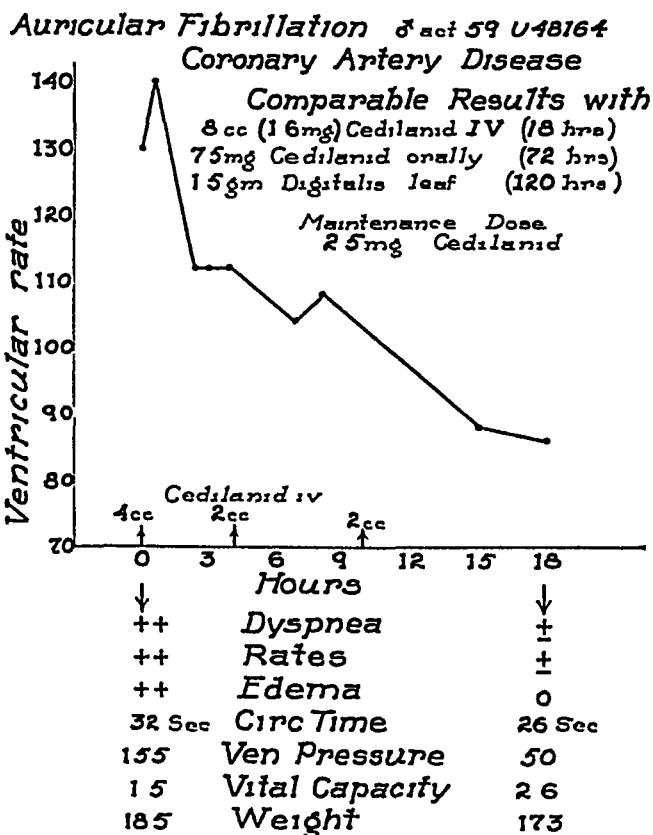


FIG 2

nocturnal dyspnea, auricular fibrillation and auricular flutter. Most of them were hospitalized. Cedilanid was given orally or intravenously after a preliminary control period of rest in bed, restriction of salt and fluids, and sedation. In many instances repeated determinations of the venous pressure,* circulation time,† and vital capacity were made to supplement the usual clinical observations of changes in dyspnea, orthopnea, cyanosis, venous engorgement, rales, cardiac rate, blood pressure, size of liver, peripheral edema,

* Venous pressure was determined by the direct method with a spinal fluid manometer.

† Circulation rates were determined with the objective alpha lobeline (Sandoz) method by injecting from 0.003 to 0.005 gm.

weight and fluid balance. These data were recorded on mimeographed charts. Repeated electrocardiograms were taken during and after digitalization in order to determine the effects on the electrocardiogram and on the rate of excretion.

The dosage of cedilanid (see Dosage, page 208) varied according to the speed desired for digitalization. The maintenance dose for both oral and

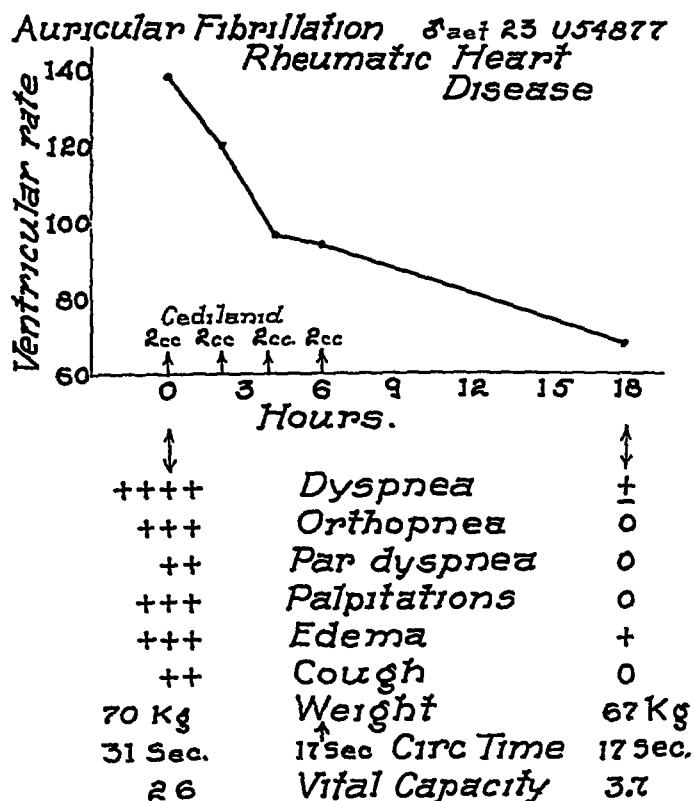


FIG 3

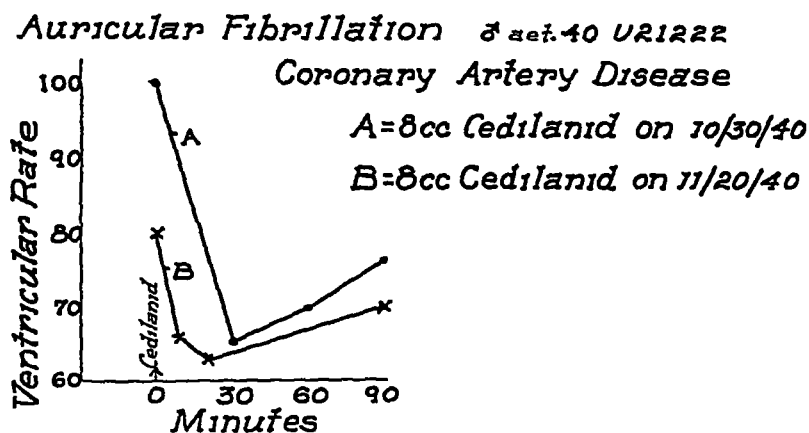


FIG 4

intravenous preparations was obtained by frequent examination of each patient over periods of months. All observations were made after the patient had been recumbent for at least 20 minutes. The maintenance dose was considered the dose just short of the point of mild toxic symptoms which could be maintained for at least a month.

Many of the patients had been previously digitalized and maintained with *Digitalis purpurea*. Some were subsequently digitalized with purpurea if failure occurred when cedilanid was omitted. In this way a comparison of the dosage, toxicity, and excretion of *Digitalis purpurea* and cedilanid was possible.

CLINICAL RESULTS

The therapeutic results with cedilanid paralleled the best previously obtained with *Digitalis purpurea*. Of 95 patients, approximately 40 per cent had cardiac failure with sinus rhythm. All but three of these received striking therapeutic benefits. They had varying degrees of failure, but the almost uniform improvement in dyspnea, orthopnea, edema and other symptoms confirms the many observations made in recent years which prove the value of digitalis in cardiac failure with sinus rhythm.

Approximately one-third of the patients had auricular fibrillation with or without failure, and all showed definite improvement. The speed of action of the drug when given intravenously was particularly noteworthy.

Auricular flutter was present in 17 instances. After administration of cedilanid, conversion to auricular fibrillation occurred in two and to sinus rhythm in 14 patients, one converted spontaneously. Frequently the conversion took place within 24 hours. The dose was the same as that given in failure. Representative charts are shown in figures 6, 7 and 8.

DOSAGE

At first the dose was determined by trial and error. When our investigation was begun, the only clinical reports were those of continental investigators. We found that their dosage was too low and that our figures came close to those of Fahr and LaDuc.¹¹

The oral digitalizing dose was determined accurately in 45 patients. It varied from 7 mg. in 24 hours to 16 mg. in 96 hours, the average dose was 7.5 mg. in 72 hours. The range of dosage is given in table 1.

TABLE 1

No. of Hours	No. of Cases	Dose mg.
24	9	4-7
48	6	5-14
72	15	5-9
96	5	6-16
> 96	9	9-16

The *intravenous* cedilanid was given in full dosage to 41 patients. Digitalization was accomplished by single or multiple injections within 24 to 48 hours. The digitalizing dose varied from 6 to 16 cc (12 to 32 mg) in 24 hours. No patient had even mild toxicity on less than 8 cc (16 mg) in 24 hours. Three patients had mild transient nausea when 8 cc were given in a single dose. Several patients received 2 cc (0.4 mg) every four hours for three to four days until full digitalization occurred. No toxic symptoms were observed and the clinical results were excellent.

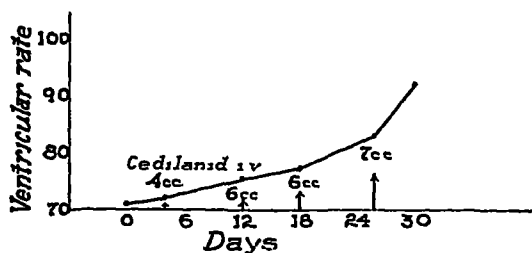
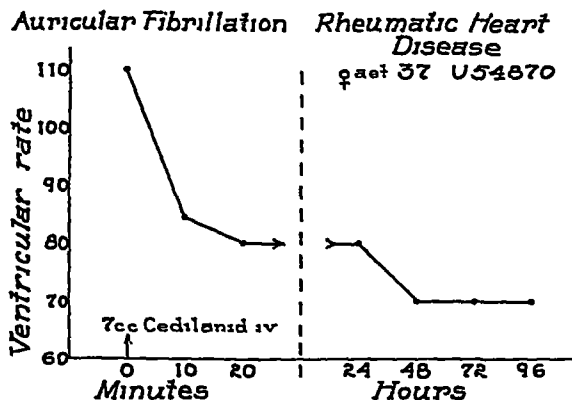


FIG 5

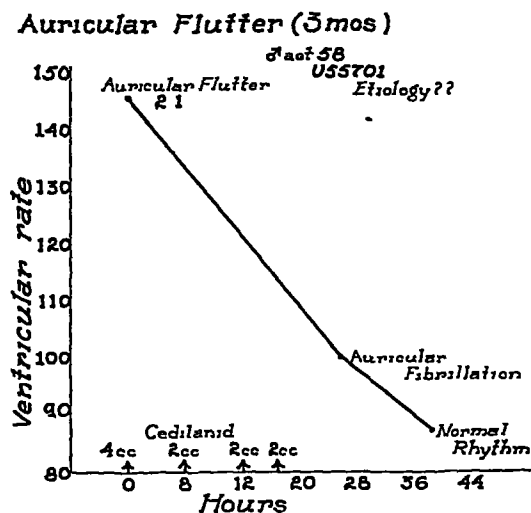


FIG 6

Striking clinical effects were obtained with the intravenous preparation. An abrupt drop in ventricular rate frequently occurred within 10 minutes (figures 4 and 5), although the full effect usually required an hour. This confirms the observations of Fahr and LaDue¹¹. In some patients the effect on the ventricular rate was not obtained until the digitalizing dose had been reached. In figure 1 it is seen that the third dose of 2 cc produced an abrupt and sustained fall in ventricular rate, whereas 6 cc previously administered had had only a partial and unsustained effect. In many instances the patient entered the hospital in desperate cardiac failure and within 24 hours showed striking subjective and objective improvement. Typical examples are shown in figures 2 and 3.

For intravenous administration of cedilanid we have found that the procedure of choice is an initial dose of 6 cc (12 mg) followed by doses of 2 cc (0.5 mg) every three to four hours until the desired beneficial or mild toxic symptoms are obtained.

The *maintenance* dose of oral cedilanid was determined accurately in 47 patients. For a period ranging from several months to two years, these patients were seen every two to four weeks and the clinical state and resting ventricular rates after administration of varying amounts of the drug were noted. The dose needed for maintenance ranged from 0.5 to 2.5 mg. The average maintenance dose was 1.6 mg.

The maintenance dose of the intravenous preparation was determined in three patients. It was 10 cc, 12 cc, and 20 cc respectively, or an average of 0.34 mg daily. Figure 5 illustrates the method of determining the maintenance dose. The patient received 23 cc over a period of a month during which time the ventricular rate gradually escaped from 70 to 90, the maintenance dose, therefore, was greater than 10 cc.

COMPARISON OF ORAL AND INTRAVENOUS CEDILANID

Accurate comparison of the digitalizing dose of the oral and intravenous preparations of cedilanid in the same patient on different occasions was made in seven patients. Table 2 illustrates the results. The average oral-intra-

TABLE II

Oral Dose (72 hours) mg	Intravenous Dose Oral/Intravenous	
	(24 hours) mg	Ratio
7.5	1.6	4.7
9.0	2.1	4.3
7.5	1.4	5.3
7.0	1.2	5.8
6.4	1.6	4.0
7.0	1.9	3.7
9.0	1.6	5.6

venous ratio is 4.8 to 1. Thus, in terms of milligrams, 4.8 times as much drug is required for oral as for intravenous digitalization. However, if we assume an average maintenance dose of 1.6 mg and correct the oral digitalizing dose to that obtained in 24 hours, the ratio is 4.4 to 1.6, or 2.75. Thus, in terms of 24-hour digitalization, 2.75 times as much drug is required for the oral as for the intravenous dose.

No significant difference in the clinical effectiveness of the oral and intravenous preparations could be determined, except with regard to the *duration* of effect. Only mild toxic symptoms were obtained with the intravenous drug whereas with the oral drug they were more severe. Further work is in progress to determine whether the effects are more constant and predictable if the drug is given intravenously. It may be the more uniform because the individual variations in absorption need not be considered.

The intravenous product is not desirable for maintenance because of its rapid excretion and the necessity for continued and frequent injections.

DURATION OF EFFECT

Approximately two to three weeks are required for subsidence of the electrocardiographic abnormalities produced by cedilanid. Re-escape of the ventricular rate in auricular fibrillation may occur in seven to eight days; the exact time was determined in only six hospitalized patients. Wide oscillations in ventricular rate for 24 to 36 hours frequently precede the fixed acceleration noted with escape. The diurnal oscillations in a well controlled ventricular rate are small. The P-R prolongation frequently disappears in three to four days. Slight residual electrocardiographic abnormalities were occasionally seen three to four weeks after the drug had been discontinued.

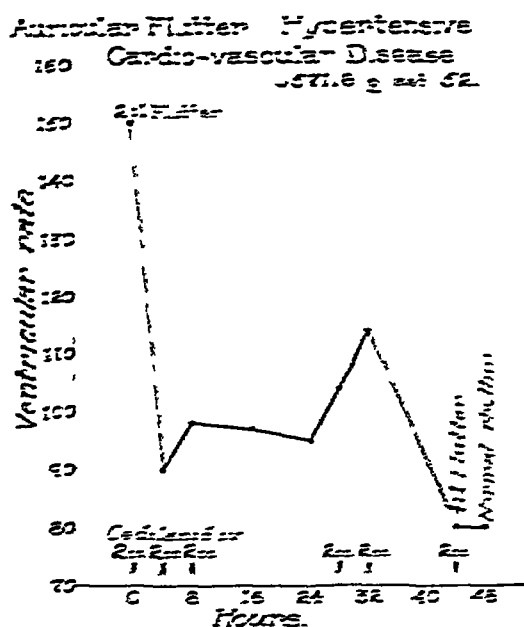


FIG. 7.

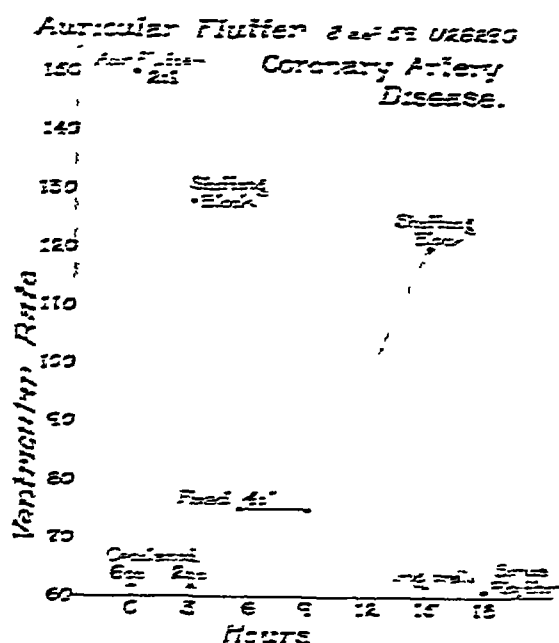


FIG. 8.

COMPARISON OF CEDILANID AND DIGITALIS PURPUREA

No significant objective difference could be seen in the effect of the oral preparations. In patients who considered either one or the other drug as superior, no significant differences could be demonstrated. Patients who failed to respond to one of the drugs did not respond to the other. Figure 9 illustrates the effects in a patient with auricular flutter who was treated with both drugs during different attacks. Patients saturated with either of the two drugs could be maintained on the other drug. These effects were observed in 44 patients.

In 21 patients accurate data on the comparative maintenance doses of cedilanid and *Digitalis purpurea* were obtained. The average maintenance doses were 1.6 mg. and 0.13 gm. respectively. This in terms of cat units is

a ratio of 5 to 1, but, as noted previously, cat units can not be used to compare crystalline and crude substances

Accurate data on the comparative digitalizing dose of the two drugs were obtained in 10 patients The average digitalizing dose in 72 hours was 7.6 mg for cedilanid and 1.5 gm for *Digitalis purpurea* This, in terms of cat units, is a ratio of 2 to 1

Auricular Flutter #51377 ♂ Age 68

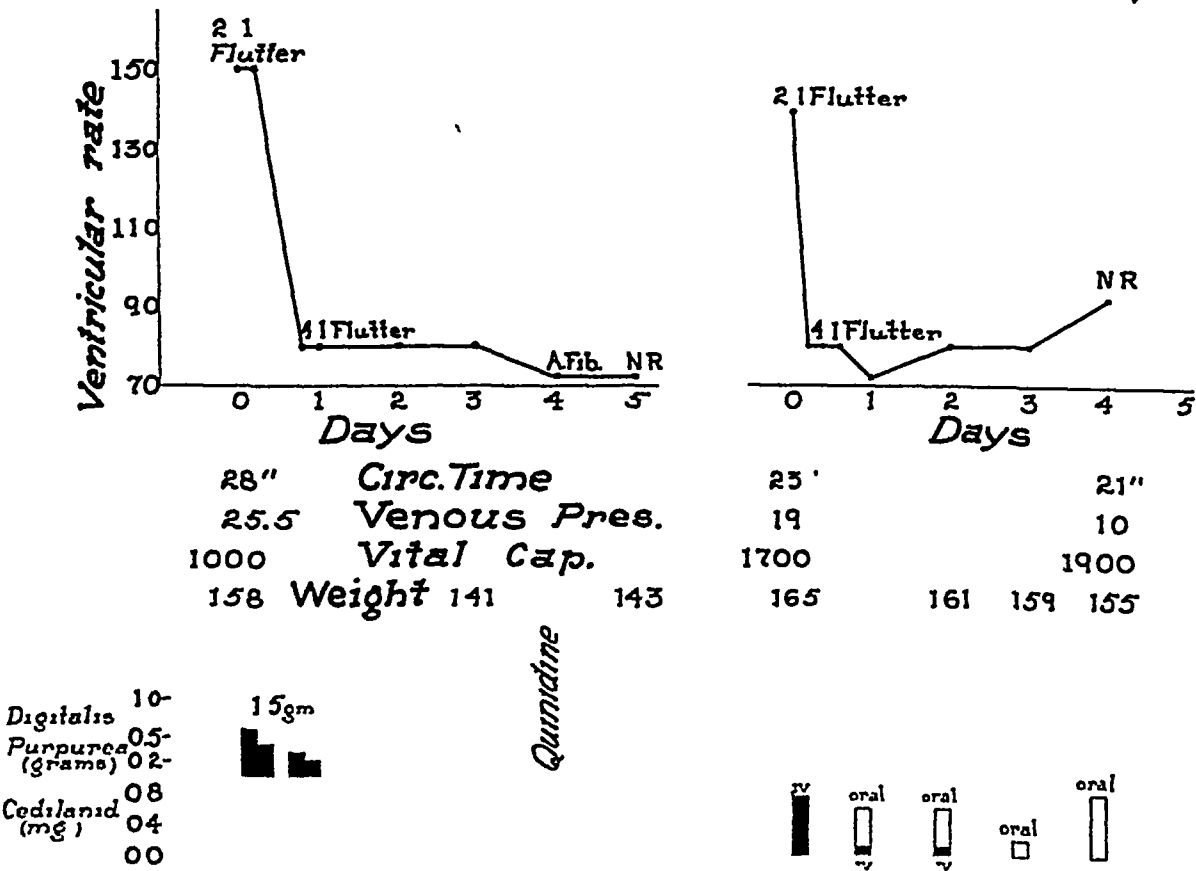


FIG 9

It is of interest to note that the digitalizing-maintenance ratio of cedilanid is 7.6 to 1.6, or 4.7, whereas that of *Digitalis purpurea* is 1.5 to 0.13, or 11.3. Thus, the maintenance dose of cedilanid is approximately one-fourth the digitalizing dose whereas the maintenance dose of *Digitalis purpurea* is one-eleventh the digitalizing dose. Therefore, it is apparent that oral cedilanid is absorbed or utilized roughly three times as easily as is oral *Digitalis purpurea*. If, as Gold¹ has stated, only 10 to 20 per cent of *Digitalis purpurea* is absorbed from the gastrointestinal tract, then 30 to 60 per cent of cedilanid is absorbed. These figures compare favorably with the doses required to digitalize one patient with both oral and intravenous cedilanid (figure 2).

According to our clinical study, the most obvious benefit of cedilanid is derived from its intravenous use in urgent cardiac failure or when rapid, ac-

curate dosage is desired. Its uniform potency and its purity allow greater confidence in giving large intravenous doses. The increased absorption of oral cedilanid may prove important.

SUMMARY

1 Lanatoside C (cedilanid) is a pure, stable, crystalline glycoside derived from *Digitalis lanata*.

2 It is a potent therapeutic agent in congestive cardiac failure with normal rhythm, in auricular fibrillation and in auricular flutter.

3 In auricular fibrillation, intravenous cedilanid produces an abrupt fall in the ventricular rate, frequently within 10 minutes.

4 The average oral digitalizing dose of cedilanid is 7.5 mg. in three days.

5 The average intravenous digitalizing dose is 8 c.c. (16 mg.) in 24 hours.

6 The average maintenance dose of oral cedilanid is 1.6 mg.

7 Oral cedilanid apparently is absorbed three times as readily as oral *Digitalis purpurea*. This is based on the fact that the digitalizing dose of cedilanid is only 4.7 times its maintenance dose whereas the digitalizing dose of *Digitalis purpurea* is 11.3 times its maintenance dose.

8 No striking difference in clinical effects was noted between oral cedilanid and oral *Digitalis purpurea*.

9 The most important therapeutic advantage of cedilanid is obtained from the intravenous preparation, primarily because of its rapid action.

10 Approximately 2.8 times as much drug is required for oral as for intravenous 24-hour digitalization.

BIBLIOGRAPHY

- 1 GOLD, HARRY. Digitalis in heart failure, *New York State Jr. Med.*, 1941, xli, 496.
- 2 SMITH, SYDNEY. II Digitalis glucosides, *Jr. Chem. Soc.*, 1930, 2478.
SMITH, SYDNEY. III Digitalis glucosides, *Jr. Chem. Soc.*, 1931, 23.
- 3 STOLL, ARTHUR. The cardiac glycosides, 1937, Pharmaceutical Press, London.
- 4 MOE, G. K., and VISSCHER, M. B. Studies on the native glucosides of *digitalis lanata*, *Jr. Pharmacol. and Exper. Therap.*, 1938, lxiv, 65.
- 5 WAYNE, E. J. Clinical observations on two pure glucosides of digitalis, digoxin and digitalinum verum, *Clin. Sci.*, 1933, i, 63.
- 6 JUNET, R., and BIANCHI, M. Etude clinique d'un nouveau digitaligal, le digilande, *Rev. med. de la Suisse Rom.*, 1939, lxx, 139.
- 7 MICHAUD, L. L'emploi du digilande C en clinique, *Schweiz. med. Wchnschr.*, 1938, lxxv, 1338.
- 8 GOLD, HARRY, KWIT, N. T., and CATTELL, McKEEN. Studies on purified digitalis glucosides. I. *Jr. Pharmacol. and Exper. Therap.*, 1940, lxx, 177.
- 9 KWIT, N. T., GOLD, HARRY, and CATTELL, McKEEN. Studies on purified digitalis glucosides. II. *Jr. Pharmacol. and Exper. Therap.*, 1940, lxx, 254.
- 10 CATTELL, McKEEN, and GOLD, HARRY. Studies on purified digitalis glucosides, III. *Jr. Pharmacol. and Exper. Therap.*, 1941, lxxxi, 114.
- 11 FAHR, GEORGE, and LADUE, JOHN. A preliminary investigation of the therapeutic value of lanatoside C (cedilanid), *Am. Heart Jr.*, 1941, xxxi, 133.

PANCREATIC TISSUE EXTRACT (INSULIN-FREE) IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

By CHARLES KLEIN, M D , GAMLIEL SALAND, M D , F A C P , and
HERMAN ZURROW, M D , *Bronx, New York*

It has become the custom, in the literature on peripheral vascular disease, to state that there has been an upsurge of interest in, and an increase in clinical and physiological understanding of this type of disorder in recent years. To those who work intensively in this field, however, it is evident that therapeutics has not kept pace with diagnosis. Moreover, the problem of treatment becomes progressively more important as our increasing understanding of peripheral vascular diseases uncovers more cases, and as our population shifts into the age group in which vascular disease is one of the commoner causes of disability.

It is our purpose, in this paper, not to introduce a new therapeutic agent, but to present the results of a three-year study of one of the first substances used in the treatment of peripheral vascular disease, namely, insulin-free pancreatic tissue extract. This substance has been used for at least 10 years. Acknowledgment for its introduction is generally accorded to Frey and Kraut¹. It has been used extensively in Europe for the treatment of angina pectoris as well as of claudication. Wolffe has contributed to our understanding of its chemical nature and physiologic action,² and he has submitted several reports concerning the clinical evaluation of its effects^{3,4}. Recently, Fisher, Duryce, and Wright described a partly objective method for evaluating the effect of therapeutic agents on claudication time and submitted a favorable report on the action of insulin-free, pancreatic tissue extract⁵.

At our Clinic, the study of pancreatic tissue extract[†] was divided into three parts. (1) Observation of the "immediate" effect, i.e., within three hours, of intramuscular injection of the tissue extract on superficial (skin) and deep (muscle) temperature. (2) Observation of the "immediate" effect, i.e., within one-half hour, of intramuscular injection of the tissue extract on claudication time, as measured by the ergometer. (3) Evaluation clinically, according to criteria set forth by us⁶ and outlined below, of the effect of prolonged, regular administration of pancreatic tissue extract by intramuscular injection, for periods varying from six to 24 months.

*Received for publication December 27, 1941.

From the Peripheral Vascular Disease Department, The Bronx Hospital, Bronx, New York.

†In our studies, three different commercial brands of pancreatic tissue extract were used. The extract designated hereafter as No. 1 is Tissue Extract No. 568 (Sharp & Dohme), that designated No. 2 is Pancreatic Hormone (Grant), No. 3 is Depropanex (Sharp & Dohme). We wish to express our appreciation to these companies for their kindness and courtesy in supplying our Clinic with these materials for clinical study.

1 *Effect on Skin and Muscle Temperature* The effect of deproteinated, insulin-free, pancreatic tissue extract (Depropanex) on the skin surface temperature of the great toe and on the calf muscle temperature was studied in nine patients. At the start of each study the patient was permitted to rest, lying on a table, with the lower extremities exposed to room temperature, which was between 21 and 26° Centigrade. An intramuscular thermocouple needle was inserted into the calf muscles of one extremity and connected with a galvanometer adjusted to give temperature readings in degrees Centigrade.* A skin thermocouple† was used to measure skin surface temperature, the area of skin on the dorsum of the great toe just below the nail base was used. Frequent preliminary readings were taken. When the skin and muscle temperatures appeared stable after at least two consecutive readings 10 minutes apart, the study was begun on the patient. One-half to one hour was usually required before temperatures no longer varied. Room temperatures were recorded, and care was taken to keep them as constant as possible. Rectal temperatures were taken before any procedure was started, and the study not done if the reading was higher than 99.8° F. Three cubic centimeters of pancreatic tissue extract were injected intramuscularly, and skin surface and muscle temperatures were recorded at approximately 15-minute intervals for from two to three hours.

The nine patients studied were taken from the Peripheral Vascular Disease Clinic. They had never been treated with pancreatic tissue extract. They all had had a complete medical and peripheral vascular workup. They consisted of two normal patients and seven patients with arteriosclerosis obliterans.

In the interpretation of results, it was considered that skin temperature changes of less than 1° Centigrade were not significant, being well within the range of technical error. Changes in surrounding environmental temperature were taken into consideration in analyzing results, as indicated below.

Results (see table 1) In eight cases, the muscle temperature fell from 0.5 to 4.1° Centigrade within two hours after the injection of pancreatic tissue extract. These eight included the two normal patients. In one case of arteriosclerosis obliterans there was a rise of 1.0°, however, in this study, the room temperature rose 3°.

In five cases, the skin surface temperature was not appreciably altered. In one case, there was a rise in temperature of the right and left great toes of 2.2 and 2.1°, respectively. This was a case of arteriosclerosis obliterans. In one case, without peripheral vascular disease, there was a rise in skin temperature of 1.0° in the left great toe. In one case of arteriosclerosis obliterans there was a drop of 3.4° in the right great toe, a drop of 2.7° in the left great toe. In another case of arteriosclerosis obliterans there was a drop of 2.7° in the right great toe, and a drop of 3.3° in the left great toe.

* Leeds-Northrup Instrument Co.

† Taylor Dermatherm

Table 1

Effect of Pancreatic Tissue Extract on Skin and Muscle Temperature

Patient's Diagnosis	Skin Temperature		Muscle Temperature		Rectal Temperature	
	Before	After	Before	After	Before	After
S. T., Arteriosclerosis obliterans	27.4	26.9	24.0	23.6	34.7	34.7
M. B., A.S.O.	27.5	24.0	27.4	24.7	32.2	30.2
J. S., A.S.O.	26.3	28.5	26.5	28.3	33.5	33.0
A. K., A.S.O.	24.4	24.9	29.2	29.8	33.6	32.5
L. P., no vascular disease	23.0	23.5	22.8	23.5	36.1	35.9
M. K., A.S.O.	22.5	22.5	22.3	22.5	34.5	34.6
M. S., A.S.O.	25.9	26.1	24.6	25.1	34.1	35
R. S., no vascular disease	22.1	22.2	22.1	21.7	36.3	34.1
C. W., A.S.O.	28.6	25.0	25.3	24.5	34.2	33.0

Summary: Of nine patients studied, a drop in muscle temperature occurred in eight cases, a slight rise in one case, within two hours after the intramuscular injection of 3 cc of pancreatic tissue extract. In five cases there was no significant alteration in skin surface temperature, a drop in two cases, a slight rise in two cases.

2 "Immediate" Effect on Claudication Time Nine patients, all suffering from arteriosclerosis obliterans, were used in this study. Four could walk no more than one-half to one city block without the occurrence of cramp-like muscle pain severe enough to require cessation of walking. Four could walk about one and one-half city blocks before the onset of claudication pain. One patient could walk 15 blocks.

Depropanex (Sharp & Dohme) was the tissue extract used, and normal saline was used as a control substance in the control studies. Measurement of the claudication time was done by means of an ergometer. This consisted, essentially, of a 10 pound weight connected with a foot pedal by means of a thin chain passing over a pulley. The patient raised this 10 pound weight six inches by depressing the pedal with his foot; by keeping the heel fixed as much as possible, this threw the greatest part of the work on the calf muscles.

The procedure used was as follows. The patient was seated before the ergometer, at rest, for one-half hour. Then, using the limb showing the greater involvement, the patient depressed the foot pedal at a fixed, regular rate until muscle pain set in. This interval was timed, and the number of times the foot pedal had been depressed in this period was read from the counter. Another half-hour rest period was given, and the ergometry was repeated. Then 3 cc of pancreatic tissue extract were injected intramuscularly, a half-hour rest period was given, and the ergometry was again repeated. One week later the above procedure was repeated in its entirety, with the same patient, using the same limb, except that 3 cc of normal saline were injected in place of the pancreatic tissue extract.

Results (see table 2) After Depropanex injection, three patients showed

TABLE II

Effect of Tissue Extract (Depropanex) on Claudication Time of 9 Patients Suffering from Arteriosclerosis Obliterans *Ergometric Measurements*

Case No	"Clinical" Claudication Distance	Depropanex				Normal Saline		
			After 1st ½-Hour Rest Period	After 2nd ½-Hour Rest Period	½ Hour After Tissue Ext Injection	After 1st ½-Hour Rest Period	After 2nd ½-Hour Rest Period	½-Hour After Saline Injection
65122	1½ blocks	Secs Strokes	186 228	211 253	254 360	162 177	289 277	282 305
109181	1½ blocks	Secs Strokes	121 121	83 96	113 126	132 142	113 121	229 314
74797	1½ blocks	Secs Strokes	261 276	— —	209 245	over 12 minutes		
82293	1½ blocks	Secs Strokes	21 7	84 10	60 33	42 41	61 71	120 100
114246	½ block	Secs Strokes	130 148	143 164	93 111	146 167	143 168	233 282
n 84081	½ block	Secs Strokes	187 167	154 167	140 156	199 235	201 285	146 177
f1 87815	Less than ½ block	Secs Strokes	72 84	63 74	73 84	75 96	99 135	93 121
ea T1 73005	15 blocks	Secs Strokes	95 114	59 75	115 121	not reported		
CO118 oblit 374	½ block	Secs Strokes	51 58	58 70	37 36	24 —	29 —	28 —
I								

a significant prolongation of claudication time (43, 33, 56 seconds, and 107, 30, 46 pedal strokes, respectively), four patients showed a decrease in claudication time (52, 50, 14, 21 seconds and 31, 53, 11, 34 pedal strokes, respectively), one patient showed practically no change (10 seconds, 10 strokes more), one patient did not adhere to the rate and rhythm set, and pedalled 23 strokes more but 24 seconds less

After normal saline (control) injection, three patients showed an increase in claudication time (116, 59, 90 seconds and 193, 29, 114 pedal strokes, respectively), one patient showed a 7-second decrease, but could pedal 28 times more, one patient showed only a 1-second difference, with pedal strokes not reported, two patients showed a decrease of claudication time (6, 65 seconds and 14, 108 pedal strokes, respectively), two cases were not reported

In summary, it could be stated that pancreatic tissue extract (Depropanex) had no specific effect in prolonging claudication time within one-half hour of injection, as measured by ergometer

3 *Clinical Evaluation of Effect of Prolonged Administration of Pancreatic Tissue Extract* Thirty-nine patients were used as subjects Of

the 5, 15 and 30 sec. periods, these were given a rest of 10 min. after each interval, or were given no interruption of any kind, but were given 15 min. rest intervals for reoxygenation and other purposes. The 30 sec. periods were given periods of 10 min. extra rest, thus were about 40 sec. per minute, minimum, 40 sec., 1 min., and 10 min., respectively. Each one of the groups received a different commercial brand of preparation for the exercise. This was given twice a week for 3 or 4 days, increasing gradually. Patients in both divisions for no extract therapy had 15 min. rest periods, and 1 instruction sheet on care of the test, but none of them received extra rest. They received local foot care and treatment at the Clinic and the attention to them, as the pediatrists, were given analgesics or sedatives for the "pain."

On admission of the patient to the Clinic a complete history was taken, physical examination was done, and routine and special laboratory tests were performed. The peripheral vascular status of the patient was then determined according to the following scheme:

(a) Vascular anatomic status. This was determined by palpation of pulses, by oscillometry, by noting temperature of extremities to touch, by determining degree of rubor on dependency, and of pallor on elevation of the limbs, and by roentgenograms of the extremities for calcification. This factor was then graded from 4-plus bilateral (severest) involvement down through 1-plus unilateral involvement (minimal changes in one limb) to 0 (no evidence of pathologic change in the blood vessels).

(b) Tissue anatomic status. This was determined by noting the degree of involvement of deep and superficial tissues, and was graded as follows: 4-plus, gangrene, pregangrene, 3-plus, ulceration, 2-plus, infection (cellulitis, lymphangitis) without gangrene, 1-plus, skin and muscle atrophy, dermatophytosis, nail disturbances, etc., 0, no apparent tissue changes.

(c) Rest pain. The patient was questioned regarding the occurrence of pain, sensations of coldness or burning, or cramping in the extremities when at rest or at night. This, if present, was recorded and graded according to intensity, from 1-plus to 4-plus.

(d) Claudication. The patient was asked how many city blocks he could walk before pain in the lower extremity set in which required that he stop and rest. This was graded as follows: 4-plus, if the patient could walk no more than one-half block, 3-plus, if he could walk one-half block to two blocks, 2-plus, two to four blocks, 1-plus, more than four blocks, but still limited, 0, no claudication.

(e) Vascular reserve, or capacity for vasodilatation. This was determined by means of the thermal reflex vasodilatation test.⁷ Where thermal test did not produce full dilatation, nerve block was performed, wherever feasible. The posterior tibial and common peroneal nerves were infiltrated with 1 to 2 per cent novocaine. Vascular reserve was graded thus. Full dilatation, or rise in skin surface temperature of dorsum of great toe to 30.5°C , was marked 4-plus. A 75 per cent rise from the initial temperature

to 30.5°, 3-plus, a 50 per cent rise, 2-plus, a 25 per cent rise, 1-plus, no rise, or insignificant rise, 0

(f) Functional classification This represented a summation of the entire disease picture, and can be explained as follows Class I, patients who have organic vascular disease without symptoms, class II, patients who have organic vascular disease (a) with minimal symptoms and (b) with moderate symptoms, class III, patients who have organic vascular disease and who are bedridden because of severe pain occurring even at rest, or because of gangrene, ulceration, or infection, class IV, patients who have symptoms of vascular disease without organic vascular disease, this last is the "functional" group

Every six months the patients in this study were given a complete workup, the previously-described grading procedure was repeated, and the results were charted for comparison

To show the clinical comparability of the control and the pancreatic tissue extract treated cases, it might be well, at this point, to append the following chart (table 3) It indicates the status of all the patients in our

TABLE III
Description of Patients Used in Study of Effect of Prolonged Administration of
Pancreatic Tissue Extract

	Tissue Ext No 1	Tissue Ext No 2	Tissue Ext No 3	Total T E	Control Case
Number of Patients	9	9	6	24	15
Sex of Patients	M 7, F 2	M 8, F 1	M 6, F 0	M 22, F 3	M 14, F 1
Age Distribution					
40 to 49	0	2	0	2	1
50 to 59	0	1	0	1	3
60 to 69	6	5	5	16	9
70 to 79	1	1	1	3	1
Etiology					
Arteriosclerosis obliterans (A S O)	8	4	4	16	10
A S O and diabetes	0	2	0	2	1
A S O and hypertension	1	1	1	3	2
A S O, diab, hypertens	0	0	0	0	1
A S O and C N S syphilis	0	1	0	1	0
A S O and late latent lues	0	0	1	1	0
Thromboangitis oblit	0	0	0	0	1
Thrombophlebitis with vasospasm	0	1	0	1	0
Vascular anatomic status (See text) (B Bilateral, U Unilateral)					
4 + B	2	4	3	9	5
3 + B	1	1	1	3	4
2 + B	1	1	1	3	4
1 + B	2	2	0	4	1
4 + U	0	0	0	0	0
3 + U	1	1	0	2	0
2 + U	1	0	0	1	0
1 + U	1	0	0	1	0
0	0	0	1	1	1

TABLE III (Continued)

	Tissue Ext. No. 1	Tissue Ext. No. 2	Tissue Ext. No. 3	Total P.E.	Control Cases
Tissue anatomic status (See text):					
4 +	1	0	0	1	0
3 +	1	1	1	3	0
2 +	1	0	0	1	2
1 +	2	2	2	6	5
0	4	6	3	13	8
Rest pain (See text):					
1 +	0	0	0	0	0
3 +	1	1	0	2	0
2 +	3	2	2	7	1
1 +	0	2	0	2	2
0	1	1	1	12	12
Claudication (See text)					
1 +	2	3	2	7	1
3 +	5	4	2	11	6
2 +	0	2	0	2	1
1 +	0	0	2	2	2
0	1	0	0	1	0
Vascular reserve (See text):					
1 +	0	1	2	6	4
3 +	2	1	2	5	3
2 +	4	1	1	6	0
1 +	1	3	0	1	2
0	2	0	1	3	6
Functional classification (See text):					
I	0	0	0	0	0
IIa.	3	1	2	6	3
IIb	3	6	3	12	9
III.	3	1	1	5	2
IV	0	1	0	1	1

series at the start of this investigation. It can be seen that, though the patients were not selected, they fit into the gradings in each category in such a manner that the percentages of control versus treated cases follow a similar distribution curve in each of the various categories. It should also be noted that all our patients were of the outpatient type, i.e., ambulatory, at the start of our investigation.

Results These (see tables 4, 5, 6) are grouped according to our findings after 6-, 12-, and 18-month periods of treatment, and are tabulated in the pattern of classification described above. Because there was no significant difference in the results obtained with the three different commercial brands of pancreatic tissue extract and because the individual figures for each brand are too small, all the results for the tissue extract treated cases are reported together.

After six months of treatment, of the pancreatic tissue extract treated cases, two out of nine (22.2 per cent) showed improvement in vascular anatomic status, two out of seven (28.5 per cent) improvement in tissue anatomic status, three out of nine (33.3 per cent) improvement in rest pain,

TABLE IV

Results of Treatment with Pancreatic Tissue Extract *After Six Months*

Aspect	No of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status					
Controls	7	4	2	1	57.1
Tiss Extr	9	2	5	2	22.2
Tissue anatomic status					
Controls	4	1	2	1	25.0
Tiss Extr	7	2	4	1	28.5
Rest Pain					
Controls	7	0	4	3	0.0
Tiss Extr	9	3	5	1	33.3
Claudication					
Controls	6	0	5	1	0.0
Tiss Extr	9	6	3	0	66.7
Vascular reserve					
Controls	7	3	1	3	42.9
Tiss Extr	20	8	7	5	40.0
Functional class					
Controls	7	2	5	0	28.5
Tiss Extr	10	4	5	1	40.0

TABLE V

Results of Treatment with Pancreatic Tissue Extract *After Twelve Months*

Aspect	No of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status					
Controls	9	2	3	4	22.2
Tiss Extr	15	3	6	6	20.0
Tissue anatomic status					
Controls	6	0	3	3	0.0
Tiss Extr	14	5	6	3	35.7
Rest pain					
Controls	7	0	4	3	0.0
Tiss Extr	14	6	7	1	42.9
Claudication					
Controls	8	2	4	2	25.0
Tiss Extr	15	10	3	2	66.7
Vascular reserve					
Controls	6	3	1	2	50.0
Tiss Extr	15	3	4	8	20.0
Functional class					
Controls	8	2	4	2	25.0
Tiss Extr	15	9	3	3	60.0

TABLE VI
Results of Treatment with Pancreatic Tissue Extract *After Eighteen Months*

Aspect	No of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status					
Controls	7	2	2	3	28.5
Tiss Extr	7	3	1	3	42.9
Tissue anatomic status					
Controls	6	2	3	1	33.3
Tiss Extr	6	2	1	3	33.3
Rest pain					
Controls	4	0	4	0	0.0
Tiss Extr	7	2	3	2	28.5
Claudication					
Controls	6	3	1	2	50.0
Tiss Extr	6	6	0	0	100.0
Vascular reserve					
Controls	5	2	2	1	40.0
Tiss Extr	7	1	2	4	14.3
Functional class					
Controls	6	3	3	0	50.0
Tiss Extr	6	4	2	0	66.7

six out of nine (66.7 per cent) improvement in claudication, eight out of 20 (40 per cent) improvement in vascular reserve, and four out of 10 (40 per cent) improvement in functional classification.

Of the control series, four out of seven (57.1 per cent) showed improvement in vascular anatomic status, one out of four (25 per cent) showed improvement in tissue anatomic status, 0 out of seven (0 per cent) showed improvement in rest pain, 0 out of six (0 per cent) showed improvement in claudication, three out of seven (42.9 per cent) showed improvement in vascular reserve, and two out of seven (28.5 per cent) improvement in functional classification.

After 12 months of treatment, of the pancreatic tissue extract treated cases, three out of 15 (20 per cent) showed improvement in vascular anatomic status, five out of 14 (35.7 per cent) showed improvement in tissue anatomic status, six out of 14 (42.9 per cent) showed improvement in rest pain, 10 out of 15 (66.7 per cent) showed improvement in claudication, three out of 15 (20 per cent) showed improvement in vascular reserve, and nine out of 15 (60 per cent) showed improvement in functional classification.

Of the control series, two out of nine (22.2 per cent) showed improvement in vascular anatomic status, 0 out of six (0 per cent) showed improvement in tissue anatomic status, 0 out of seven (0 per cent) showed improvement in rest pain, two out of eight (25 per cent) showed improvement in claudication, three out of six (50 per cent) showed improvement in vascular reserve, and two out of eight (25 per cent) showed improvement in functional classification.

After 18 months of treatment, of the pancreatic tissue extract treated cases, three out of seven (42.9 per cent) showed improvement in vascular anatomic status, two out of six (33.3 per cent) showed improvement in tissue anatomic status, two out of seven (28.5 per cent) showed improvement in rest pain, six out of six (100 per cent) showed improvement in claudication, one out of seven (14.3 per cent) showed improvement in vascular reserve, and four out of six (66.7 per cent) showed improvement in functional classification.

Of the control series, two out of seven (28.5 per cent) showed improvement in vascular anatomic status, two out of six (33.3 per cent) showed improvement in tissue anatomic status, 0 out of four (0 per cent) showed improvement in rest pain, three out of six (50 per cent) showed improvement in claudication, two out of five (40 per cent) showed improvement in vascular reserve, and three out of six (50 per cent) showed improvement in functional classification.

Summarizing these figures, one could say that the patients who were treated with pancreatic tissue extract regularly, in 3 c.c. doses twice a week for long periods of time (six to 18 months), showed improvement in claudication time and rest pain. It is interesting to note that our control cases consistently showed a greater improvement in vascular reserve than the tissue extract treated cases, as measured by thermal test or nerve block.

It should be stated here that, throughout our entire period of observation, we encountered no untoward systemic reaction in any patient following the intramuscular injection of any of the three brands of tissue extract used, a moderate number of patients complained of local pain or discomfort, of short duration, at the site of injection.

CONCLUSIONS

1. Pancreatic tissue extract, insulin-free, produced a drop in the muscle temperature of the lower extremity, with no significant effect on the skin temperature, when injected intramuscularly.

2. Pancreatic tissue extract, insulin-free, had no effect on claudication time, as measured by ergometer, within one-half hour of intramuscular injection.

3. Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to 18 months, produced improvement in claudication time and rest pain.

4. Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to 18 months, had no effect on vascular anatomic or tissue anatomic status, on vascular reserve, or on functional classification.

5. Patients receiving no specific treatment but following instructions concerning hygienic care of the feet, showed a definite degree of improvement in vascular reserve, as measured by thermal test or nerve block.

REFERENCES

- 1 FREY, EMIL K, and KRAUT, HEINRICH Über einen von der Niere ausgeschiedenen, die Herztätigkeit anregenden Stoff, *Ztschr f phys Chem*, 1926, clvii, 32
- 2 WOLFFE, JOSEPH B The therapy of tissue extract, *Trans Am Therap Soc*, 1931, xxxi, 31
- 3 WOLFFE, JOSEPH B, FINDLAY, DONALD, and DESSEN, EDWARD. Treatment of angina pectoris with a tissue vasodilator extract Preliminary report, *ANN INT MED*, 1931, v, 625
- 4 WOLFFE, JOSEPH B Pancreatic extract (enzyme-free) in the treatment of diabetic and arteriosclerotic gangrene, *Am Jr Surg*, 1939, xliii, 109
- 5 FISHER, MARTIN M, DURYEE, A WILBUR, and WRIGHT, IRVING S Deproteinized pancreatic extract (Depropanex), *Am Heart Jr*, 1939, xviii, 425
- 6 SALAND, G, KLEIN, C, ZURROW, H, GOOTNICK, A, and KATZ, A Criteria for the classification and diagnosis of peripheral vascular diseases, *Arch Int Med*, 1940, lxxv, 1035
- 7 SALAND, G, KLEIN, C, and ZURROW, H The thermal reflex vasodilatation test in peripheral vascular disease, *Am Heart Jr*, 1939, xvii, 581

CASE REPORTS

CALCINOSIS AND SCLERODERMA WITH PARATHYROIDECTOMY *

By CHARLES S. BYRON, M.D., F.A.C.P., and SAUL MICHALOVER, M.D.,
Brooklyn, New York

ROSENBERG¹ has recently reviewed the clinical features of "chalk gout." This condition, variously described as "calcinosis conscripta," "calcinosis universalis," "calcinosis syndrome," "tendino-fasciitis calcarea rheumatica," "tendinitis calcarea," "petrificatio cutis," "calcinosis interstitialis," "Raynaud's disease with calcareous degeneration," and "subcutaneous calcareous granulomata," had been previously extensively surveyed by Durham,² Steinitz,³ Weissenbach, Basch and Basch,⁴ Brooks,⁵ Rothstein and Welt,⁶ and Atkinson and Weber.⁷

In summary one may say that calcinosis is characterized by deposits of calcium in greater or lesser amounts in the skin and subcutaneous tissues. A circumscribed type is restricted to the region of the joints of the terminal phalanges and the extensor portions of the elbows and knees. A diffuse or universal type may involve extensive portions of the body surface and at times the interstitial tissue of muscle, tendon and nerve sheaths. Steinitz reports that the circumscribed syndrome is more prevalent in the elderly and more frequent in the female, the universal type in a much younger age group. Ramsdell⁸ states that the latter occurs usually in the first two decades of life. In 40 per cent of the patients scleroderma and sclerodactylia are present. Vasospastic phenomena are common. The bones and joints are not as a rule involved, although deposits and contractures about the joint may limit motion.

The pathogenesis is unknown. Two theories explaining the calcium deposits are generally held. The first implies a primary alteration in calcium metabolism, and the second holds that calcium is deposited in previously degenerated connective tissue. Neither theory is conclusively demonstrated.

The treatment is unsatisfactory. Various physical and surgical procedures, dietary measures, and the administration of hormones and drugs have been equally unsuccessful. Ramsdell's⁸ recent presentation of four patients with calcinosis universalis, demonstrating rapid reabsorption of the calcium deposits with improvement in the clinical picture following parathyroidectomy and hemithyroidectomy led us to the study of the calcium metabolism in our patient. The findings and the effects of parathyroidectomy are herein presented.

CASE REPORT

L. M. was first admitted to the hospital in 1932 at the age of 24. Her family and past history were not pertinent. Her best weight, noted at the age of 20, was 130 pounds. Menstruation had begun at 12, it recurred every 28 days, lasted four days, and was regular. She had been married four years but had never been pregnant.

* Received for publication December 20, 1941.

From the Endocrine Division, Department of Medicine, Jewish Hospital of Brooklyn.

Her present complaint was first noted at the age of 13, 11 years before admission. The first evidence of abnormality was the appearance of hard nodules on the left ring finger. One of these was excised at a hospital. Thereafter similar nodules appeared on both hands, feet, knees and the left elbow, varying in size from that of a small pea to that of a cherry. Some of these nodules would approach the surface and break down, discharging milky substance through the resultant sinus.

For two years prior to admission a progressive stiffness of the neck and upper extremities had been developing. At the same time, difficulty in opening the mouth was experienced. The patient thought that her skin was growing darker.

On admission, the patient appeared undernourished and weighed 96 pounds. The spine was rigid. The head was held erect but was raised with considerable difficulty. The skin of the face, neck, upper chest and arms had a glossy, indurated mottled brown appearance. It did not wrinkle. The lips were somewhat retracted.

The thyroid was palpable.

The arms were thin and displayed a loss of power with a bilateral wrist drop. Hard nodules, some of them freely movable, were noted in the hands. Similar lesions were present at the knee and in the feet. There was limited movement at the small joints, which tended to be flexed.

The systolic pressure was 104 mm Hg, the diastolic was not obtained.

Laboratory Data The urine, except for an occasional red blood cell and white blood cell, was negative, and the specific gravity was 1.032. The blood count was normal.

Basal metabolic rate was minus 7 per cent.

Blood chemistry was normal. The phosphorus varied from 2.1 to 3.4 mg per cent. Wassermann and Kahn reactions were negative.

On roentgen-ray, increased density was noted in the skull, femora and pelvis. Mottling of the upper third of both humeri was apparent. In some places there were areas of osteocondensation. Subcutaneous calcium deposits were seen in both hands, about the left elbow, both knees, particularly the left, over the head of the fourth metatarsal and over the middle of the right mandible.

A nodule together with some skin was removed from the knee. The nodule consisted of calcium 55 per cent and urates 10 per cent.

A biopsy report was as follows: "Superficial epidermal layer normal. The pigmented basal layer of the corium is very pronounced. The subcutaneous tissue is thickened by an increase of fibrous tissue. The hair follicles, sebaceous glands and sweat glands appear normal. In the deeper layer of the fibrosed tissue are spaces containing granular amorphous material. This contains occasional plaques of degenerated cells. The amorphous material takes a faint blue stain and is apparently soluble in Zenker's solution."

Following discharge from the hospital the patient attended the out-patient department for one year. Here she received some urinary gonadotropins and foreign proteins without perceptible effect. From 1933 to 1939 she attended another clinic. There minute amounts of anterior pituitary extract, thyroid extract, ammonium chloride and a ketogenic diet were haphazardly administered. No improvement was noted. Recurrent nodules formed and motion in the hands became more limited.

The patient was readmitted to the Jewish Hospital in November, 1939. The general nutrition was fair, weight was 116 pounds. The skin of the face was reddish brown in color and exhibited several irregular darker areas over the forehead and cheeks. It was glossy, indurated, and did not wrinkle. The mouth was drawn into a fixed smile, could not be completely closed, and could be opened only to a limited degree (figure 1). The skin over the neck, upper chest and arms, as well as over the knees, had the same sclerodermatous appearance. The muscles of the neck and arms were atrophied. Bilateral wrist drop was present. The head was held erect but

could be raised only with difficulty. The whole spine was stiff and evidenced limitation of motion. There was also some limitation of motion at the shoulders, elbows, hips and knees. The hands were kept flexed. Here, too, movements at the small joints were limited apparently by the collections of bony hard nodules in the subcutaneous tissue about them, and also by contractures due to tendon sheath involvement. Similar nodules varying from 1 to 3 cm in size, conglomerate in some areas, were found on the wrists, left elbow, sole of the right foot and knees and over the dorsal spine. There were discharging sinuses over the left knee and spine. The discharge appeared purulent and somewhat chalky.



FIG 1 Patient. Illustrating fixity of skin, atrophy and pigmentation

The blood pressure was 140 mm Hg systolic and 90 mm diastolic.

The remainder of the physical examination was not pertinent. Roentgenography revealed the heart and lungs to be negative.

Rarefaction of both humeri was noted (figure 2). There was decreased thickness of the cortex and some cystic change in the upper half of the right cortex. There was thinning of the humeroscapular articulation. All the other bones appeared normal. Calcium deposits were seen in both hands (figure 3), knees, particularly the left, over



FIG 2 Decalcification Humerus



FIG 3 Calcium deposits about phalanges and wrist

the right third, fourth and fifth metatarsals and the left fifth metatarsal. Larger deposits were evident in the subcutaneous tissue of the left elbow (figure 4) and left knee. The bones and the joints in the region were not involved. A large deposit of calcium was seen within the abdomen opposite the fourth and fifth lumbar vertebrae.

Laboratory Data Electrocardiograph showed some evidence of myocardial involvement. Basal metabolic rate was minus 14 per cent. Sedimentation time was 28 mm per hour.

Urine Specific gravity 1.020–1.030, albumin 1 plus to none, occasional white blood cell.



FIG 4 Calcium deposits about elbow

Blood Hemoglobin 94 per cent, red blood cells 6,000,000, white blood cells 19,400, 75 per cent polymorphonuclears, no abnormal cells. Kline test was negative.

Chemistry Sugar 78 mg per cent, urea 9.9 mg per cent, uric acid 4.7–5 mg per cent, lipids 650 mg per cent, cholesterol total 248, free-67 mg per cent. Urea clearance was normal. There was no arsenic in the blood. Arsenic in the urine was normal. Calcium 10.6 mg per cent, phosphorus 3.8 mg per cent, phosphatase 3.9 units, non-protein nitrogen 28.4 mg per cent, total protein 7.09 gm, albumin 4.83 gm, A/G ratio 2.14, magnesium 2.3 mg, total base 140 milli-equivalents.

The patient was discharged and returned the following month in January, 1940. Calcium and phosphorus balance studies on weighed analyzed diets were performed. These revealed a positive calcium balance and a tendency toward a negative phosphorus balance. The urinary and fecal excretion percentages for calcium were normal (table 1).

On January 12, 1940, under avertin and nitrous oxide-oxygen-ether anesthesia a right hemithyroidectomy and parathyroidectomy was performed by Dr. H. Louria. Two parathyroid glands identified histologically were removed. Sclerodermatous skin and muscle biopsies were taken. The patient made an uneventful recovery. She was discharged eight days postoperatively. The calcium and phosphorus remained normal. The uric acid seven days postoperatively was 2.9 mg per cent as compared with 5 mg preoperatively.

TABLE I
Balance Studies

Date	Calcium Intake (in mg)	Output (in mg)		Total	Balance
		Urine	Feces		
1-10-40	1218	55	663	718	+500
1-11-40	996	37	500	537	+459
1-12-40	527	74	127	201	+326
Operation, 1-12-40					
1-17-40	333	44	212	256	+ 77
1-18-40	737	62	(Feces Lost)		
1-19-40	698	67			
1-20-40	875	47	269	316	+559
Date	Phosphorus Intake	Output		Total	Balance
		Urine	Feces		
1-10	494	368	296	664	-172
1-11	1020	235	624	859	+161
1-12	494	350	164	514	- 20
Operation, 1-12-40					
1-17	431	209	187	396	+ 35
1-18	768	294	(Feces Lost)		
1-19	652	142			
1-20	695	178	111	289	+406

Histology. Two normal parathyroid glands Normal thyroid tissue

"Specimen from the sternothyroid muscle shows pink staining tissue in which the striations of the muscle are indistinct and the muscle fibers appear somewhat swollen, the larger blood vessels show some thickening of the walls and narrowing of the lumina No cellular infiltration

"The sternomastoid muscle shows hyalinizing fibrous connective tissue and adipose tissue and an occasional fragment of striped muscle The capillaries are engorged and there are foci of freshly extravasated blood There is in places a slight scattering of small round cells and large mononuclear cells

"Skin In the preparation the surface is somewhat corrugated and is covered by a narrow band of stratified squamous epithelium with keratinizing superficial layers and short blunt rete pegs Some of the cells of the basal layer contain brown pigment In places hair follicles, sebaceous glands and sweat glands are seen in the corium The superficial lymph spaces are narrow and about some of them there is a slight infiltration by small round cells, large mononuclear cells, an occasional plasma cell and eosinophile Some of the smaller blood vessels are engorged Some of the papillae are missing With the elastic tissue stain, elastic tissue is seen to be unaffected"

Postoperative Course During the first week after operation the patient noted increased facial mobility The lips could be approximated about a glass, and the forehead could be slightly wrinkled This improvement unfortunately was not progressive Two months after operation symptoms of dullness and lack of concentration made their appearance At the same time a profuse hair growth over the extremities occurred The symptoms were relieved by thyroid medication The hair growth too, became less noticeable

Roentgenograms taken seven months postoperatively revealed no change in the calcium deposits nor in the appearance of the right humerus

At the present time, 22 months after parathyroidectomy, there has been little change. Facial rugae are slightly more prominent. The tongue can be protruded to a greater degree. The scleroderma, nodules and contractures are unaltered. From time to time there is a discharge of milky fluid from one of the knee sinuses. The uric acid is 3.6 mg per cent, calcium 11.4 mg per cent, phosphorus 3.6 mg per cent, phosphatase 2.4 units.

COMMENT

Investigation of this patient failed to involve the parathyroids in the pathogenesis of calcinosis. The only suggestive findings were a preoperative tendency toward a negative phosphorus balance and the findings of changes in the right humerus resembling those seen in osteitis fibrosa cystica. The calcium balance was positive. The bone changes might be explained on the basis of disuse atrophy, since there was definite limitation of motion and atrophy of the arm muscles.

The histological appearance of the skin taken from the knee in 1932, however, suggests a more probable etiology, that is, the deposit of calcium in previously degenerated tissue. However, biopsy of sclerodermatous skin from the neck taken seven years later failed to reveal any calcium. Degenerated muscle tissue likewise exhibited no calcium deposits. It seems, then, that in addition to the usual factors of favorable ionized calcium concentration, pH, CO_2 , electrolyte and protein concentration and blood flow necessary for calcium deposit, the presence of some other factor, perhaps an enzyme, is required. What rôle the uric acid may play in the process gives rise to some speculation. A preoperative blood uric acid of 5 fell to 2.9 postoperatively. We have previously observed an elevated uric acid return to normal in two cases of hypercalcemia following parathyroidectomy. One of these proved to be an adenoma of the parathyroid, the other leukemia. Both were complicated by renal insufficiency.

The failure of clinical improvement and calcium reabsorption after operation further tends to eliminate the thyroid-parathyroid mechanism from the pathogenesis, still bearing in mind the possibility that thyroid administration might have interfered with such recovery. It is possible that in Ramsdell's cases the creation of a relative hypothyroidism interfered with the absorption of calcium from the gastrointestinal tract, so that the abnormal deposits were called upon to furnish calcium for the usual physiological processes. Yet the preoperative basal metabolic rate was definitely depressed in two of his patients, on the minus side in another and elevated in the fourth. In the postoperative course there was no reference to the development of hypothyroid phenomena. In our patient the hypothyroid symptoms interfered with her comfort, happiness and efficiency to such a degree that, having noted no clinical improvement after two months, we were forced to prescribe thyroid. The excess hair growth, we believe, can be ascribed to the thyroid underactivity.

SUMMARY

A patient presenting calcinosis universalis, scleroderma and sclerodactylia, and muscle atrophy is presented.

Studies of the calcium metabolism revealed no abnormality. The phosphorus metabolism study revealed a tendency toward a negative balance.

Hemithyroidectomy and the removal of two parathyroids, histologically identified, had little influence on the clinical course and no effect on the calcium deposits

BIBLIOGRAPHY

- 1 ROSENBERG, E F Chalk gout, Jr Am Med Assoc, 1940, cxv, 1791
- 2 DURHAM, R H Scleroderma and calcinosis, Arch Int Med, 1928, xlii, 467-490
- 3 STEINITZ, HERMANN Calcinosis circumscripta ("Kalkgicht") und Calcinosis universalis, Ergebn d inn Med u Kinderh, 1931, xxxix, 216-275
- 4 WEISSENBAACH, R J, BASCH, GEORGES, and BASCH, MARIANNE Essai critique sur la pathogénies des concrétions calcaires des sclerodermies (syndrome de Thibierge-Weissenbach) et des syndromes voisins, Ann de méd, 1932, xxxi, 504-529
- 5 BROOKS, W D W Calcinosis, Quart Jr Med, 1934, xxvii, 293-319
- 6 ROTHSTEIN, J L, and WELT, SARA Calcinosis universalis and calcinosis circumscripta in infancy and in childhood, three cases of calcinosis universalis, with review of the literature, Am Jr Dis Child, 1936, lxi, 368-422
- 7 ATKINSON, F R B, and WEBER, F P Cutaneous and subcutaneous calcinosis, Brit Jr Dermat., 1938, 1, 267-310
- 8 RAMSDELL, E G . (a) Calcinosis universalis, Proc. Am Assoc for the Study of Goiter, 1935 (b) Parathyroidectomy for the calcinosis syndrome, Proc Am Assoc for the Study of Goiter, 1939

COR PULMONALE WITH BILATERAL ANEURYSMS OF THE PULMONARY ARTERY, INTERVENTRICULAR SEPTAL DEFECT, PATENT DUCTUS ARTERIOSUS AND TERMINAL AYERZA'S SYNDROME

By M W JOHANNSEN, M D, and CHARLES A R CONNOR, M D,
New York, N Y

ANEURYSMS of the pulmonary artery are so rare as to constitute almost a curiosity. From 1905 to the present time there have been 28,180 autopsies in Bellevue Hospital and in only one case was this lesion found. The literature has been reviewed by D'Aunoy and E von Haam¹ and by Boyd and McGavack². We have found two cases out of 111 collected with lesions similar to the one here described. One was reported by Sachs³ and the other by Scott⁴.

CASE REPORT

The patient (S H) in whom we found this lesion at necropsy was a 44-year-old Hungarian housewife. She was admitted on January 9 to the Third (New York University) Medical Division, Bellevue Hospital, because of severe hemoptysis which allegedly occurred a few hours before entrance. Her past history was uneventful. Though examined many times by physicians, she had never been told of heart disease. Four months before admission, friends called her attention to the blueness of her lips, but not until the last six weeks did she experience any symptoms. At that time she noticed dyspnea on effort, fatigue and cough. She consulted a physician who ad-

* Received for publication November 26, 1940

From the Laboratories of Pathology and the Third (New York University) Medical Division, Bellevue Hospital

ministered digitalis and told her that her blood pressure was high. Despite treatment, her symptoms increased and she sought hospitalization following the onset of hemoptysis.

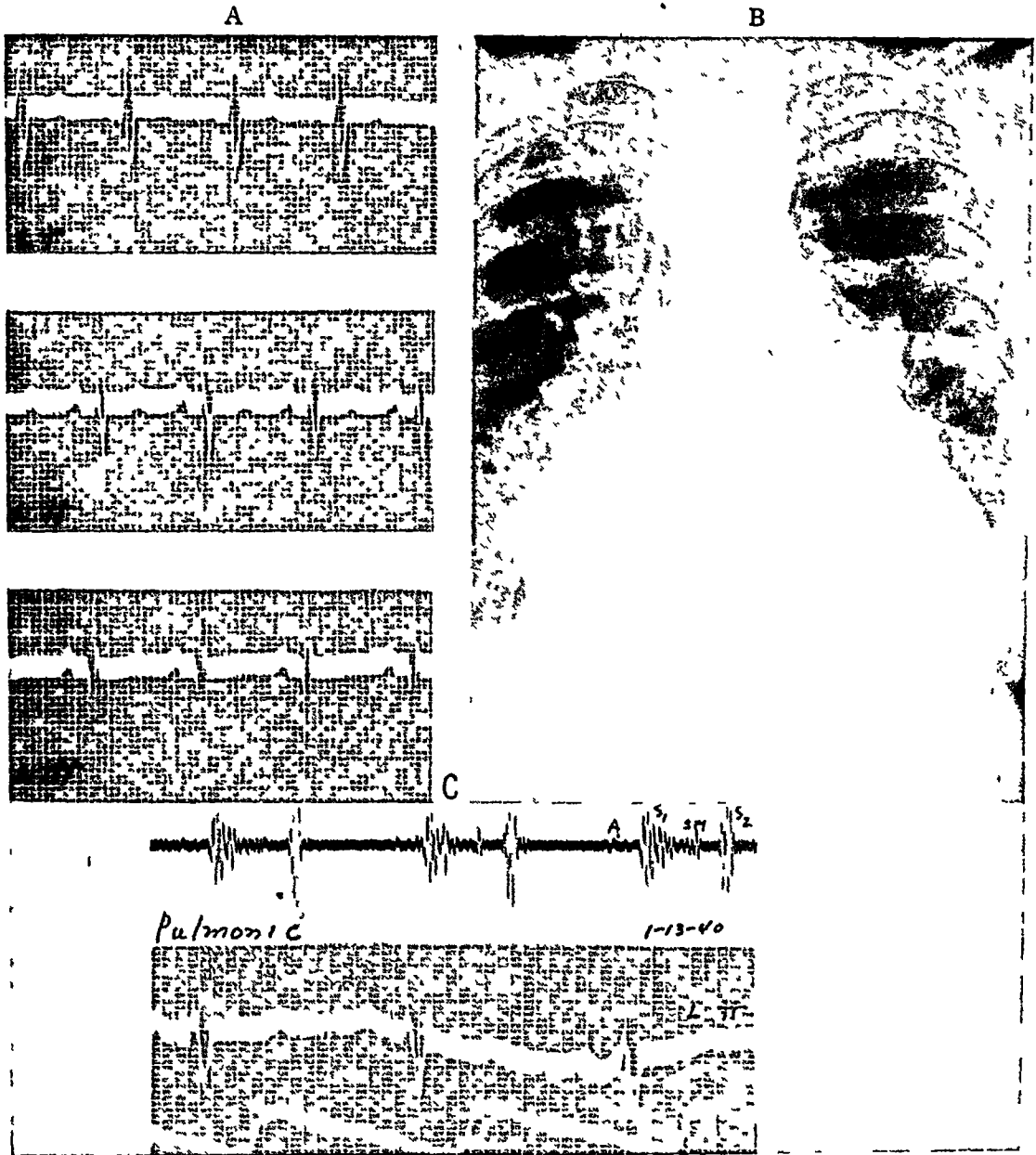


FIG 1 A Electrocardiogram showing normal sinus rhythm and marked right axis deviation B Teleroentgenogram showing the tremendous enlargement of both the right and left sides of the heart. The calcification of the pulmonary vessels is also evident C Stethogram showing the systolic murmur immediately following the first heart sound. The accentuated second pulmonic sound. The short diastolic murmur following this sound.

She was a small, under-developed but well nourished, white female with cyanosis of the entire body. She was dyspneic and orthopneic. She coughed frequently, raising blood streaked sputum. The jugular veins were distended and filled from below. The lungs were clear, except for a few rhonchi over the right lower lobe.

posteriorly. The heart was greatly enlarged. The impulse at the apex was forceful and was seen in the fifth intercostal space in the anterior axillary line. There was a loud, harsh systolic murmur heard both at the apex and base. A short diastolic murmur was audible along the upper part of the left sternal border. The second pulmonic sound was accentuated. The rhythm was regular. The systolic blood pressure was 160 mm Hg and the diastolic 108 mm Hg. The liver was palpated about 5 cm below the costal margin. The spleen was not felt. There was a moderate amount of dependent edema of the lower extremities and in the sacral region. The fingers and toes showed slight clubbing.



FIG 2 View of right ventricle A showing (patent) interventricular septal defect. Note hypertrophy of right ventricular wall at B.

The admission urine showed proteinuria. The specific gravity was 1.013 and there were many white blood cells in the sediment. The red blood cells numbered 7.14 million, hemoglobin 22 grams (154 per cent), leukocyte count and differential smear were normal. The blood Wassermann reaction was negative. Non-protein nitrogen was 53 mg. per cent, creatinine 2.6 mg. per cent. The venous pressure, taken by the direct method, was 28 cm. of water. The electrocardiogram (figure 1A) showed normal sinus rhythm and marked right axis deviation. The stethogram (figure 1C) was interpreted as recording an accentuated second pulmonic sound, a systolic murmur at the apex, aortic and pulmonic areas, and a short diastolic murmur at the pulmonic area. The teleroentgenogram (figure 1B) disclosed generalized cardiac enlargement, most marked along the right border and the outflow tract of the right ventricle. Dilatation and calcification of the right and left pulmonary arteries were evident. The left lung base was obscured by the enlarged heart shadow, at the base of the right lung were numerous small areas of increased density. The upper half of the left lung was emphysematous. Oxygen determination of arterial blood showed 30 volumes

per cent saturation, a second sample the following day after she had been kept in an oxygen tent in which the oxygen tension was maintained between 60 and 70 per cent, showed 62 volumes per cent saturation. Despite continued oxygen therapy and redigitalization there was no change in her condition. Four days after admission she became weak and comatose, the blood pressure fell to 80 mm Hg systolic and 50 mm diastolic, the heart sounds, however, remained loud. She died in coma on the ninth day after admission.

The significant postmortem findings were as follows. The abdomen contained 50 c.c., the left pleural cavity 300 c.c., and the pericardial sac 250 c.c. of clear yellow fluid. All the viscera showed evidence of chronic passive congestion.



FIG 3 A, Opening of ductus arteriosus B, Aneurysm of left pulmonary artery. Note the organizing thrombus extending into the branch supplying the left upper lobe C, Ostium of right pulmonary artery

The heart was markedly enlarged both to the right and left. The apex was formed by both ventricles, the right ventricle forming about two-thirds of the anterior surface. The pericardial surface was smooth and the membrane thin. There was slight increase in the epicardial fat. The right auricle was dilated and its walls thickened. The tricuspid valves were normal in texture. Their chordae tendineae were not deformed. The right ventricle was dilated and its muscle hypertrophied, measuring at its widest portion 1.5 cm. There was a defect in the interventricular septum (figure 2) immediately below the auriculoventricular junction, measuring 0.8 cm. The foramen ovale was closed. The pulmonic ring was normal in size. The pulmonary valves were thin.

The left auricle was dilated and its wall slightly thickened. The leaflets of the mitral valve were thin and the mitral ring measured 10 cm in circumference. The left ventricle was dilated, its musculature was 1.2 cm thick. The aortic leaflets

showed no naked-eye changes. There were no intra-aortic or intraventricular thrombi. The coronary arteries revealed slight intimal thickening. There was no myocardial fibrosis.

The aorta was diminished in caliber and measured 3 cm in diameter, it contained numerous small yellowish plaques. Its elasticity was well preserved. There was no evidence of syphilis. The arch communicated with the pulmonary artery through a widely patent ductus arteriosus (figure 3) which measured 1.2 cm in diameter and 1 cm in length. Its pulmonary ostium was located 4 cm above the pulmonary cusps and was at the site of bifurcation of the pulmonary artery, cephalad to the right pulmonary artery.



FIG 4 After cutting the aorta and turning the edges back, the aneurysm of the right pulmonary artery is exposed. A glass rod (C) is approximately 3 centimeters above the lower level of the aneurysm. A indicates the patent ductus arteriosus, B, aneurysm of the left pulmonary artery, and D, the interventricular septal defect.

The pulmonary conus, pulmonary artery and its branches exhibited a moderate, and in places a severe, degree of atherosclerosis with calcification. The left pulmonary artery (figure 3) was dilated prior to its entrance into the lung. This aneurysmal dilatation measured 2.5 cm in diameter. Its wall was thin and the aneurysm was filled by a gray, laminated clot, which extended into the branch supplying the left upper lobe. This branch was also dilated, measuring 1.2 cm in diameter. Many of its smaller rami were either completely or partially occluded by continuation of the above described thrombus. The extrapulmonary part of the right pulmonary artery (figure 4) was also dilated, forming a sac which had a depth of 3 cm and a length of 3.2 cm. Its lumen was partially obliterated by an organized and organizing thrombus. The branch to the right lower lobe was occluded by similar blood elements. Posteriorly this aneurysm was identified by its size and upward displacement of the bifurcation of the trachea.

We believe that the two congenital arteriovenous shunts necessitated increased work on the part of the right ventricle. These shunts were also largely responsible for the pulmonary hypertension shown, clinically, by the right sided cardiac enlargement and the accentuated pulmonic second sound and, anatomically, by the right ventricular hypertrophy (cor pulmonale). This hypertension plus other unknown factors was in turn partially responsible for the degree of arteriosclerosis and calcification of the pulmonary vessels. The presence of arteriosclerosis and persistence of the ductus Botalli were undoubtedly the important factors in the development of the aneurysm of the right and left pulmonary arteries.

Furthermore, the occurrence of thrombi in the aneurysms and the gradual occlusion of many of the pulmonary vessels contributed to failure of the right side of the heart, to the increased venous pressure, and to polycythemia and progressive anoxia. It is likely that until the onset of her symptoms the patient had adequate compensation for the two arteriovenous shunts despite the partial occlusion of many of the pulmonary arteries. When the right ventricle was no longer able to maintain its output, there was reversal of flow through the ductus arteriosus and the interventricular septal defect. This accounts for the terminal cyanosis and inability to obtain a higher level of arterial oxygen saturation even under optimal external conditions.

During the last few days of her life this patient showed the syndrome described by Brenner⁵. These individuals may exhibit few or no symptoms despite the presence of widespread thrombosis of the pulmonary arteries and then expire suddenly or within a few days owing to the complete occlusion of the already narrowed vessels.

BIBLIOGRAPHY

- 1 D'AUNOY, R, and VON HAAM, E. Aneurysm of the pulmonary artery with patent ductus arteriosus, Jr Path and Bact, 1934, xxviii, 39
- 2 BOYD, L J, and MCGAVACK, T H. Aneurysm of the pulmonary artery, Am Heart Jr, 1939, xviii, 562
- 3 SACHS, R. Weit offener ductus Botalli mit Bildung von (nichttuberculösen) Lungenarterienaneurysm, Deutsch med Wchnschr, 1892, xviii, 446
- 4 SCOTT, RONALD B. Aneurysm of the pulmonary artery, Lancet, 1934, i, 567
- 5 BRENNER, O. Sclerosis of the pulmonary artery with thrombosis, Lancet, 1931, i, 911

SULFUR DIOXIDE CHEMICAL PNEUMONIA, REPORT OF A CASE WITH RECOVERY FOLLOWING ACCIDENTAL EXPLOSION OF A REFRIGERATOR UNIT *

By HAROLD L. GOLDBURGH, M D, F A C P, and BENJAMIN A. GOULEY, M D,
Philadelphia, Pennsylvania

It is apparent that with increasing industrialization man is surrounding himself with ever increasing health hazards. Of these, one of the most important is the inhalation of irritating gas. Physicians became aware of its effect on the bronchopulmonary system during the first World War when poison gas was em-

* Received for publication August 6, 1941

ployed as a weapon. Exposure has since become increasingly common in association with numerous chemical developments in industry. One of these is the use of sulfur dioxide in modern refrigeration. The toxic effects of this gas have been noted in recent reports dealing with occupational disability in the refrigerating and sulfur mining industries. These investigations were concerned mainly with the results of long continued inhalation of small amounts of the gas.¹ Chronic bronchitis and increased susceptibility to colds have been common sequelae of such exposure. Needles and Smith² reported on the late effects of acute sulfur dioxide poisoning in a patient who came under their observation with widespread tubular bronchiectasis and sharply reduced respiratory function. Martini, Dossola and Celener³ have recorded the first death caused by chemical pneumonia due to sulfur dioxide poisoning. We wish to report a similar case with recovery, exemplifying (1) the rapidly destructive effect of concentrated sulfur dioxide inhalation, and (2) the apparently beneficial result of sulfonamide therapy.

CASE REPORT

B. B., aged 15, was admitted to the Jewish Hospital November 11, 1940. The history revealed that he had found a refrigerator unit on a vacant lot and that while dismantling it, the tank blew up in his face. Further investigation showed that the fumes consisted of sulfur dioxide.

Upon admission to the accident ward about 15 minutes after the accident, the boy was very weak, dyspneic, hoarse, and unusually cyanotic. The temperature was 102.4° F, the pulse rate 140, the respiratory rate 42 per minute. There was considerable edema of the eyelids with chemosis. Widespread erosions of the conjunctivae, the nose and mouth attested to the severity of the chemical burns. The larynx was inflamed, its mucosa eroded, but there was no obstruction of the glottis. The rapid respiratory rate, the limitation of expansion in the left lower lobe, the impaired percussion note over both bases and the presence of many inspiratory râles, particularly over the left lower lobe, all indicated a rapidly progressive bronchitis and bronchiolitis. The heart was not displaced. Its action was regular but very rapid, and the sounds were of reduced volume. No murmurs were heard. The abdominal examination was negative.

Early signs of consolidation were apparent within 12 hours and flank consolidation was present in 24 hours.

Forty-eight hours after admission a roentgenogram showed a localized area of haziness obscuring the left costophrenic sulcus and extending up to the ninth rib. The roentgenologic appearance was that of a basal bronchopneumonia associated possibly with a diaphragmatic pleurisy.

The patient was placed in an oxygen tent because of his dyspnea and cyanosis. Dehydration was combated by daily venoclysis of 2000 cc of 5 per cent glucose in normal saline solution. The patient also received a transfusion of 250 cc citrated blood. He was given sulfathiazole, receiving 11 grams in 36 hours, at which time the blood concentration of the drug was 3.3 mg per cent. The temperature began to decline from its high level of 104° and was normal on the fifth day of therapy, after 25 grams of sulfathiazole had been given. At this time the signs of pulmonary consolidation disappeared, but residual bronchitis was evident.

Roentgen-ray examination on November 25 revealed that the pneumonia had undergone complete resolution, but some intensification of the bronchial markings at the right base was evident.

Laboratory examination on November 12 showed 67 per cent hemoglobin, 3,700,000 erythrocytes, 17,600 leukocytes, of which 93 per cent were polymorphonuclears.

In the absence of productive cough, no sputum examination was made. Throat cultures revealed streptococci, staphylococci and pneumococci. The latter were type 22, a "high number type" of doubtful significance. A blood culture remained negative. There was no evidence of renal disturbance. The indirect van den Bergh was slightly elevated to 0.75 mg per cent. (At no time was clinical jaundice noted.) We were unable to make any tests for sulfhemoglobin in the blood.

The boy was discharged on November 26, although it was thought that the cyanosis had not entirely disappeared.

Following his discharge he remained intermittently under our observation (H. G.). He suffered frequent attacks of lacrimation and sneezing. Hoarseness and cough persisted. The latter, worse in the night, was associated with morning expectoration of thick, greenish, purulent sputum. Night sweats persisted for two weeks after leaving the hospital, but there was apparently no fever except for a period of one week during the Christmas holiday. The boy complained of nervousness and extreme fatigue which prevented his return to school until early in January 1941. The school authorities thought that he had become mentally retarded.

On February 1, 1941, a roentgenogram revealed definite intensification of the lung markings in both lower lobes, especially the right. At his last follow-up examination in April 1941, the boy complained of lacrimation, although no gross conjunctival change was noted. A posterior ethmoiditis and hyperplastic pharyngitis were present. The cough and morning expectoration continued apparently unassociated with fever or weight loss. Transient râles were heard at both lung bases. In view of the continued morning expectoration of purulent sputum and the roentgenographic appearance of the lungs, bronchiectasis was considered to be present in both lower lobes. Bronchography was advised but was not done.

DISCUSSION

Sulfur dioxide, widely used in refrigeration, is considered ideal for that purpose in that it is non-explosive and non-inflammable⁴. It is, however, one of the most irritant gases, so much so that Alice Hamilton considered it irrespirable and thus massive exposure impossible insofar as the respiratory tract is concerned⁵. This is not altogether true as evidenced by the experience of others^{2, 3} as well as ourselves. In fairly high concentration the gas is corrosive, forming sulfuric acid on combining with water. Its destructive action on the moist surfaces of mucous membranes is thus explained.

Sulfur dioxide is thus similar in its action to nitrogen dioxide and tetroxide which, combining with water, give rise to another corrosive acid, namely, nitric acid⁶. Although experimental work on sulfur dioxide poisoning has not been extensive as in the case of nitrogen tetroxide and the war gases, it is believed that the pathologic changes are fundamentally alike in most of these irritant gases, possibly in all of them⁷. The great damage caused by them in both experimental animals and man is in the bronchi and bronchioles, with erosion of the lining epithelium, deciliation, edema of the underlying submucosa, spasm of the bronchial muscle and thrombosis of the small arteries and veins^{6, 8}. With inhalation of concentrated fumes, the acute process extends into the alveolar ducts and the alveoli. In the latter, the inflammatory exudate consists of fibrin and plugs of desquamated cells resembling a picture of the so-called lobular catarrhal pneumonia. However, uniform lobar involvement may occur both experimentally and clinically. Death may come quickly, i.e., on the first day, as a result of pulmonary edema, somewhat later because of pneumonia. Survival over many days allows bronchial and alveolar regeneration, often attended, however,

with striking epithelial metaplasia,^{6, 9} bronchial necrosis, bronchiolitis obliterans, bronchiectasis.² The acute erosive changes and the subsequent alterations in the course of regeneration favor bacterial invasion of the lung parenchyma. Coplin in discussing the delayed deaths in war gas poisoning said that he never saw a case in which bacteria were not abundant in the lungs, noting especially the common incidence of streptococci and gas bacilli. The latter point is important inasmuch as bacterial invasion was once not considered essential to the development of chemical pneumonia.¹¹

These observations on the pathological changes are pertinent to the clinical and therapeutic considerations of such cases as our own. Our patient is one of the few instances, apparently the second recorded case, and the first to recover of acute chemical pneumonia caused by sulfur dioxide. The symptomatology of these two cases was practically identical in its abrupt and explosive development with that noted in numerous cases of nitrogen tetroxide poisoning, and it seems reasonable to discuss them as a group in the light of recent therapeutic advances. One is impressed with the high mortality figures in reports of nitrogen tetroxide poisoning. Schubert (1911) collected 213 cases, of which 55 were fatal (24 per cent).¹² In those cases in which pneumonia was definitely present, the mortality was much higher, being 100 per cent in many small series of cases.^{13, 14} The majority of these victims died within four days of exposure, often within 48 hours. The marked cyanosis and dyspnea, the rapid course, and the picture of "medical shock" are reminiscent of what was seen in the 1917-1918 pandemic of influenza. In this connection, the resemblance of the pathologic findings was commented on by Winternitz.^{8, 15} The important common factors were apparently the swift local destruction of respiratory surface barriers and the subsequent collapse of resistance to mixed bacterial invasion. Physicians today possess a therapeutic weapon theoretically adequate for such a situation, namely the sulfonamide drugs, which by their bacteriostatic action on many types of organisms allow time for the patients' recuperation and the development of humoral defense.

The administration of sulfathiazole to a patient with sulfur dioxide poisoning presented a therapeutic problem. In view of the patient's cyanosis the presence of sulfhemoglobinemia was a possibility and is considered by some to be a contraindication to sulfonamide therapy. In retrospect, we believe that sulfathiazole was highly effective. It is to be noted that in the case of Martin and Dossola, an 18 year old boy previously in good health, modern therapy consisting of oxygen, intravenous administration of glucose and saline, and a fair degree of digitalization was of no avail. A comparison based on single cases or even on small groups is inconclusive, but the data herein presented suggest that sulfonamide therapy in chemical pneumonia may be beneficial and should be administered early in effective dosage. In the absence of spectroscopic examination, the presence of sulfhemoglobin in our case remained questionable. It was noted above that early and often striking cyanosis is common to nitrogen tetroxide, chlorine and bromine pneumonitis. Occasional spectroscopic examinations, clinical and experimental, have shown that methemoglobinemia is not the cause of the cyanosis.^{14, 16} The latter is due apparently to acute exudative edema interstitially and in the alveoli causing acute anoxemia.

Chronic Sequelae With a single exception,¹⁷ clinical reports agree on the bad chronic effect, chiefly on the bronchi, resulting from sulfur dioxide inhala-

tion These reports are based on long range observations in the industries in which an increasing incidence of "colds," bronchitis and dyspnea has been noted despite an increasing tolerance shown by many workmen incidental to long continued exposure¹⁸ In occasional constitutionally susceptible individuals bronchial asthma appears to have followed such exposure^{19, 20} Acute poisoning, if survived, should almost certainly lead to chronic bronchitis Bronchiectasis was observed by Needles and Smith, and our patient is apparently following a similar course Koontz,²⁰ basing his conclusion solely on experimental animal work, thought dogs that survived acute chemical inflammation of the respiratory tract usually made a complete recovery It is doubtful whether such laboratory findings are entirely applicable to man Clinical observation suggests otherwise Bronchiectasis once established ordinarily presents a difficult therapeutic problem It may well be that sulfonamide therapy, employed in our case with apparently striking benefit, might have been utilized in suitable dosage with equally important results in the later afebrile and subchronic stages It is clear that bronchiectasis progresses mainly by reason of persistent infection, and prolonged small dosage of the sulfonamides may conceivably have another useful field in such cases as our own

SUMMARY

Concentrated sulfur dioxide inhalation may lead to acute inflammation of the respiratory tract, culminating in "chemical" pneumonia After such exposure, a boy, aged 15, previously well, quickly showed signs of bronchopulmonary involvement Cyanosis and dyspnea were notable features Sulfathiazole therapy contributed to recovery, but its use limited to the acute phase of the illness did not prevent the later development of bronchiectasis

The almost fatal accident leading to this illness was caused by the dismantling of a discarded refrigerator unit The existence of such hazards should be publicized

Since this article was submitted for publication, the following case has been observed

G T, aged 46, a junk dealer, was admitted to the Jefferson Hospital, Philadelphia, on October 6, 1941, to the surgical service of Dr George P Muller The patient gave a history of hammering an old refrigerator unit which exploded with the sudden release of a gas which was considered to be sulfur dioxide The patient was brought to the hospital within 15 minutes following the accident At this time there were evidences of first degree burns of the face, eyes, nose and throat

He complained of marked chest pains He had a fever of 102° F and a leukocyte count of 17,900 per cu mm A pneumonitis was suspected Dr Hobart Reimann found a few scattered râles in the right lower lobe The roentgen-ray report on October 9, 1941 revealed "prominence of the hilar and parenchymal markings bilaterally, a little worse on the left side as is seen in tracheo-bronchitis"

Since his discharge on October 14, 1941 he has complained of postnasal dripping, cough and substernal pains, and the expectoration of thick mucopurulent sputum He has become "nervous," that is, he frequently has felt "light-headed" and confused when driving his car None of these symptoms existed prior to his accident

He is being observed for any progressive changes in his lungs, especially early bronchiectasis

BIBLIOGRAPHY

- 1 KEHOE, R A, MACHLE, W F, KIR/MILLER, K, and LeBLANC, T J On effects of prolonged exposure to sulphur dioxide, Jr Indust Hyg, 1932, xiv, 159-173
- 2 SMITH, F J, and NEEDLES, R J Bronchiectasis, late effect of acute sulphur dioxide poisoning with report of a case, Trans Am Clin and Climatol Assoc, 1939, liii, 109-116
- 3 MARTINI, T, DOSSOLA, A, and CEIENFR, D Intoxicacion aguda por gas sofocante (anhidrido sulfuroso), Semana méd, 1940, i, 110-112
- 4 McNALLY, W D Use of sulphur dioxide as refrigerant, Indust Med, 1939, viii, 234-238
- 5 HAMILTON, A Industrial poisons in the United States, 1925, Macmillan and Co, New York, p 324
- 6 WOOD, F C Poisoning by nitric oxide fumes, Arch Int Med, 1912, x, 478-504
- 7 HAGGARD, H W Action of irritant gases upon the respiratory tract, Jr Indust Hyg, 1924, v, 390-398
- 8 WINTERNITZ, M C Anatomical changes in the respiratory tract initiated by irritating gases, Mil Surgeon, 1919, xlv, 476-493
- 9 PAPPENHEIMER, A M Discussion of the paper by Winternitz¹⁵
- 10 COPIIN, W M L Ibid¹⁵
- 11 DELAFIELD, F, PRUDDEN, T M, and WOOD, F C Textbook of Pathology, 1919, Wm Wood & Co, New York, p 698
- 12 SCHUBERT Ueber Nitrose-Vergiftungen, Ztschr f Med-Beamte u Krankh, 1911, xxiv, 557-568
- 13 LOESCKE Beitrage zur Histologie und Pathogenese der Nitritvergiftungen, Beitr z path Anat u z allg Path, 1910, xlix, 457-475
- 14 SAVELS, A Zur Kasuistik der Nitrosen-vergiftung durch Inhalation von Salpetriger-saure, Deutsch med Wchnschr, 1910, xxxvi, 1754-1756
- 15 WINTERNITZ, M C Chronic lesions of the respiratory tract, initiated by the inhalation of irritating gases, Jr Am Med Assoc, 1919, lxxiii, 689-691
- 16 CRAMER, G Die Lungenentzündung durch gasformige Stickoxyde (nitrose Gas), Arch f Gewerbepath u Gewerbehyg, 1938, ix, 1-12
- 17 KENNON, B R Report of a case of injury to skin and eyes by liquid sulphur dioxide, Jr Indust Hyg, 1927, ix, 486-487
- 18 HUMPERDINCK, K Effects of chronic exposure to sulphur dioxide gas, Arch f Gewerbepath u Gewerbehyg, 1940, x, 4-18
- 19 DOWLING, H F Asthma following prolonged exposure to sulphur dioxide, Med Ann District of Columbia, 1937, vi, 299-300
- 20 ROMANOFF, A Sulphur dioxide poisoning as cause of asthma, Jr Allergy, 1939, x, 166-169

SUBACUTE BACTERIAL ENDARTERITIS COMPLICATING PATENT DUCTUS ARTERIOSUS. CASE REPORT WITH RECOVERY FOLLOWING SULFAPYRIDINE- HEPARIN THERAPY *

By WILLIAM A WINN, M D, CLARA L HUGHES, M D, and
JEWELL M SANDERS, M D, *Springville, California*

THE following case report of recovery from subacute bacterial endarteritis is presented because it marks the successful application of the treatment of this

* Received for publication December 16, 1941
From Tulare-Kings Counties Joint Tuberculosis Hospital

usually fatal infection by combined sulfapyridine and heparin therapy. The first announcement of this ingenious combination treatment was made by Kelson and White in 1939¹. With the publication of further controlled studies² a definite feeling of optimism begins to appear in the medical attitude toward the unfortunate patient afflicted with an endocardial or endarterial infection due to *Streptococcus viridans* (alpha type). In the case herein reported there was the further factor of a tuberculous infection manifested by the presence of *Mycobacterium tuberculosis* in the sputum. It is interesting to observe that the chemotherapy had no deleterious effect upon the pulmonary tuberculous infection which also apparently healed. During the period of observation after discharge from the hospital (12 months), the patient has remained in excellent health, and subsequent blood cultures have remained sterile.

CASE REPORT

Mrs. B. D., a 45-year-old, white, American housewife, was admitted to the Tulare-Kings Counties Joint Tuberculosis Hospital on July 12, 1940 by ambulance.

The chief complaint was unexplained fever of 11 weeks' duration associated with a slightly productive chronic cough.

The patient had enjoyed fairly good health and had always worked hard until the first part of the year 1940. In January a rectal fistula had been excised by her local physician. This healed readily but left some weakness of the sphincter. She had always been bothered by episodes of rapid heart beat and "skipping of the heart" following exertion such as fast walking or the playing of games, as "far back as she could remember." Occasionally this rapid heart rate became quite irregular and persisted for as long as one to two days.

Eleven weeks prior to admission, on the night of April 22, she was awakened in the early hours of the morning by a chill followed shortly by fever and pain on both sides of the lower chest, aggravated by breathing. The "bronchial tubes felt raw and irritated" and a rather persistent cough developed, productive of slight amounts of yellow mucoid sputum. Her family physician was called and advised the patient to remain in bed, which she did for the next week. At this time she was found to have a temperature varying from 99° F in the mornings to 101° F in the afternoons. Intermittent chills and night sweats continued, and she became very ill. Roentgenograms revealed only "old scars" in the lung fields.

At the end of a week she had failed to improve and was sent to a consultant in a nearby city. Roentgenograms of the chest were taken and an "unresolved pneumonia" disclosed in the right lower lobe. Several roentgen treatments were given over the thorax anteriorly followed by only temporary improvement and later a return of the fever which rose to 105° F in the afternoons and was accompanied by mental confusion.

The patient returned to her home. Occasional productive cough persisted with daily temperature elevation to 101° F in the afternoons. She was unable to eat and became very weak. After another week at her home she was taken to a private hospital for a day where a physician took roentgenograms, following which she again returned home.

She remained in bed at home for the next several weeks with no evidence of improvement and then was removed to the local county hospital. There a blood transfusion was given following which she became stronger. After a week's observation she was referred to the Tulare-Kings Counties Joint Tuberculosis Hospital with a diagnosis of pulmonary tuberculosis.

During this illness she had lost 30 pounds in weight (170 to 140). There was occasional shortness of breath. Chills, fever and night sweats had continued. Oc-

casional respiratory pain was noted in the lower right side of the chest. Cough occurred only occasionally and was productive of a small amount of mucoid sputum. There had never been any blood-tinged sputum. There was no history of headache, joint pains or skin lesions. Occasional vomiting had occurred after forced feeding, there was no persistent nausea.

Past History The patient was born in Missouri where she resided until the age of 36 and then came to California. Measles, chickenpox, mumps and scarlet fever (moderately severe) were reported to have occurred during childhood. She had had influenza in 1923.

At the age of 22 she was treated for "inflammatory rheumatism" over a period of six to seven months, with accompanying reddened, swollen and painful knee joints. The family physician stated that "she had had rheumatism long enough to have had a rheumatic heart." Attacks of tonsillitis were frequent during the winter months before coming to California.

Her maximum weight had been 180 pounds.

There was no history of pneumonia, pleurisy or hemoptysis. There had been no known exposure to tuberculosis. There was no history of dyspnea, orthopnea, or swelling of the feet or ankles.

Family History The patient's father, aged 72, living and well, had arthritis. Her mother, aged 70, living and well, had diabetes mellitus and arthritis. Three siblings were living and well. There was no history of familial tuberculosis, cardio-renal disease, rheumatic fever, or thyroid disease.

Marital History The patient's first husband was living and well. A daughter, aged 28, and a son, aged 26, were living and well. She had remarried at the age of 44. The second husband was living and well.

Social History The patient had been occupied as housewife, mother, cafe operator and hotel housekeeper. She had done only her own housework since her remarriage two years previously.

Physical Examination (following admission) A well developed brunette woman of middle age, lying flat in bed, obviously ill and complaining frequently. The nose and mouth had a cyanotic tinge. The skin was sallow, dry, and somewhat loose. The mucous membranes were pale and slightly cyanotic. Blood crusts were present upon the septal mucous membrane. The tongue was furred. Nearly all the molar teeth were missing, the remaining ones were sound. The tonsils were adherent and cryptic, containing a few yellowish plugs. No petechiae were noted.

The thorax was thick walled and short. Examination of the heart was as follows. Point of maximum impulse was 1 cm. to left of the midclavicular line in the fifth inter-space, it was rather forceful in character. Left border of dullness was 9 cm. from the midsternal line. The right border of dullness was only slightly outside the sternal margin. A systolic murmur was present along the left sternal border. A continuous type murmur was present in the pulmonic area, of loud whirring "machinery" type during systole. Pulmonic second sound was accentuated and louder than the aortic second sound. The heart sounds were of fairly good quality. No thrills were detected. The rhythm was regular, rate 90 per minute. The pulses were equal, of good volume, regular rate and rhythm. The vessel walls were soft. Blood pressure was 125 mm. Hg systolic and 75 mm. diastolic.

Lungs There was limited expansion of the entire right side of the chest. Tactile fremitus was slightly decreased over both bases. Resonance was diminished over these same areas. The breath sounds on the right side were of decreased intensity and of bronchovesicular character. Scattered crepitant râles were heard beneath the right scapula and in the right axilla. A few coarse râles were heard at the left base posteriorly and anteriorly. Whispered voice was slightly increased over the right base, unchanged on the left. Diaphragmatic excursion was limited on the right side.

The abdomen was rotund, with soft, obese walls. There were a few striae albicantes. The lower edge of the liver was just palpable beneath the right costal margin. The spleen was slightly enlarged. There were no areas of tenderness.

The extremities showed evidence of weight loss. The nail beds were faintly cyanotic. There was no curvature or clubbing of the fingernails. An old, healed scar tract extended into the anal opening. Digital examination was negative.

The temperature was 101.2° F, respiratory rate 20, pulse rate 90. An occasional cough occurred, with little or no production of sputum.

During the few days following admission the patient felt better but continued to have frequent, mild chills and a temperature varying from 98° F to 101° F and 103° F daily. A roentgenogram of the chest made on July 13, 1940, the day after admission (figure 1), revealed irregular patches of consolidation in the lower two-thirds



FIG 1 Roentgenogram of chest taken on admission, July 13, 1940

of the right lung field and in the left base. Old fibrosis was also present in the lower third on the right. There were calcified pulmonary foci outside the left hilus. The heart lay transversely, and there was prominence of the pulmonary conus. The aortic knob protruded and showed evidence of calcification. The impression was pneumonitis of unknown etiology, chronic passive congestion and cardiac dilatation and hypertrophy.

A specimen of sputum obtained three days after admission was concentrated and tubercle bacilli demonstrated by the Ziehl-Neelson stain (Gaffky II). The Gram stain revealed large numbers of gram-positive cocci in chains. The Kline reaction was negative.

Examination of the urine showed a light cloud of albumin, and microscopically there were 40 to 50 red blood cells and 8 to 10 white blood cells per high power field. A few coarse granular casts were also noted.

The red blood cell count was 5,100,000, and there were 12 gm of hemoglobin (7 per cent Sahli) per 100 c.c. The white blood cell count was 13,450 with mature neutrophils 76 per cent, immature 6 per cent, lymphocytes 13 per cent and monocytes 5 per cent. The red blood cells were essentially normal in size and appearance. The blood sedimentation rate (Brooks) was pathologic with 37 per cent settling at the end of 60 minutes.

On July 17, 1940, five days after admission, a blood culture was made which after five days' incubation revealed a pure growth of *Streptococcus viridans* (alpha). This was confirmed a few days later by a second culture taken on July 22, 1940, which contained 13 colonies of *Streptococcus viridans* per c.c. on the blood agar plate.

Following the demonstration of tubercle bacilli in the sputum and *Streptococcus viridans* in both blood cultures, a diagnosis of active pulmonary tuberculous infection was considered, plus patent ductus arteriosus complicated by subacute bacterial endocarditis (arteritis (*Streptococcus viridans* (alpha))). The pulmonary pathology was considered the result of septic embolic phenomena arising from the vegetative endarteritis of the ductus arteriosus. In this respect the roentgenogram was quite typical of bilateral basal pulmonary infarcts. The extent of the pulmonary tuberculous infection was considered to be very minimal and difficult to delineate by the roentgenographic appearance.

Reference to figure 2 will disclose the further important laboratory studies during the course of treatment. It graphically illustrates the temperature reaction to the bloodstream infection and the response to different sulfonamide therapies.

On July 23, 1940, the twelfth day of hospitalization, sulfanilamide was started as indicated in figure 2. This was followed in 24 hours by nausea, vomiting, increasing cyanosis, vertigo and mental confusion. The blood pressure fell to 100 mm Hg systolic and 60 mm diastolic, and there was little response to the therapy although a blood concentration of only 6 mg per cent was reached. Therefore, it was discontinued on the fourth day.

A week later the patient appeared slightly improved and less toxic. The cardiac murmurs persisted unchanged, the blood pressure rose to 110 mm Hg systolic and 60 mm diastolic. She had a return of the sharp pleuritic pain at the left pulmonary base, relieved by strapping the chest. Because of the increasing secondary anemia, she was transfused with 500 c.c. of citrated blood on the twenty-third day of hospitalization and placed on iron and vitamin B therapy.

During the following three weeks she gradually failed, becoming more toxic and showing persistent cyanosis. There was occasional cough productive of a slight amount of mucoid sputum. She continued to complain of frequent chest pain in the left base and once in the right apex.

A second chest roentgenogram, taken on August 24, 1940, showed evidence of clearing and decrease in the size of the areas of consolidation on the right side. The heart remained generally enlarged and the vascular markings accentuated in both hili.

On the forty-ninth day there was a marked secondary anemia. The urinary findings were continuously abnormal with persistent microscopic hematuria and albuminuria. A third blood culture, made on August 29, 1940, disclosed 10 to 12 colonies of *Streptococcus viridans* per c.c. During the afternoon of this day the patient complained of sudden severe precordial pain accompanied by mild orthopnea and decrease in pulse volume. There was moderate cyanosis of the face and she appeared apprehensive. The pain gradually became less severe but persisted for 36 hours. No pericardial rub could be heard, but a coronary embolic phenomenon was considered possible. A second transfusion was given.

On the following day sulfathiazole was begun followed by a drop in temperature and the onset of nausea and vomiting. After 36 hours, conjunctivitis appeared, associated with small conjunctival hemorrhages and edema of the eyelids. A rash, beginning on the index fingers, spread to the arms, thighs, legs, and forehead and became so marked and painful that the drug was discontinued after three days of use. A fourth blood culture taken at this time was positive for *Streptococcus viridans*, there being one colony per c.c. (sulfonamide present in blood). Red cells, white cells, albumin and casts persisted in the urine.

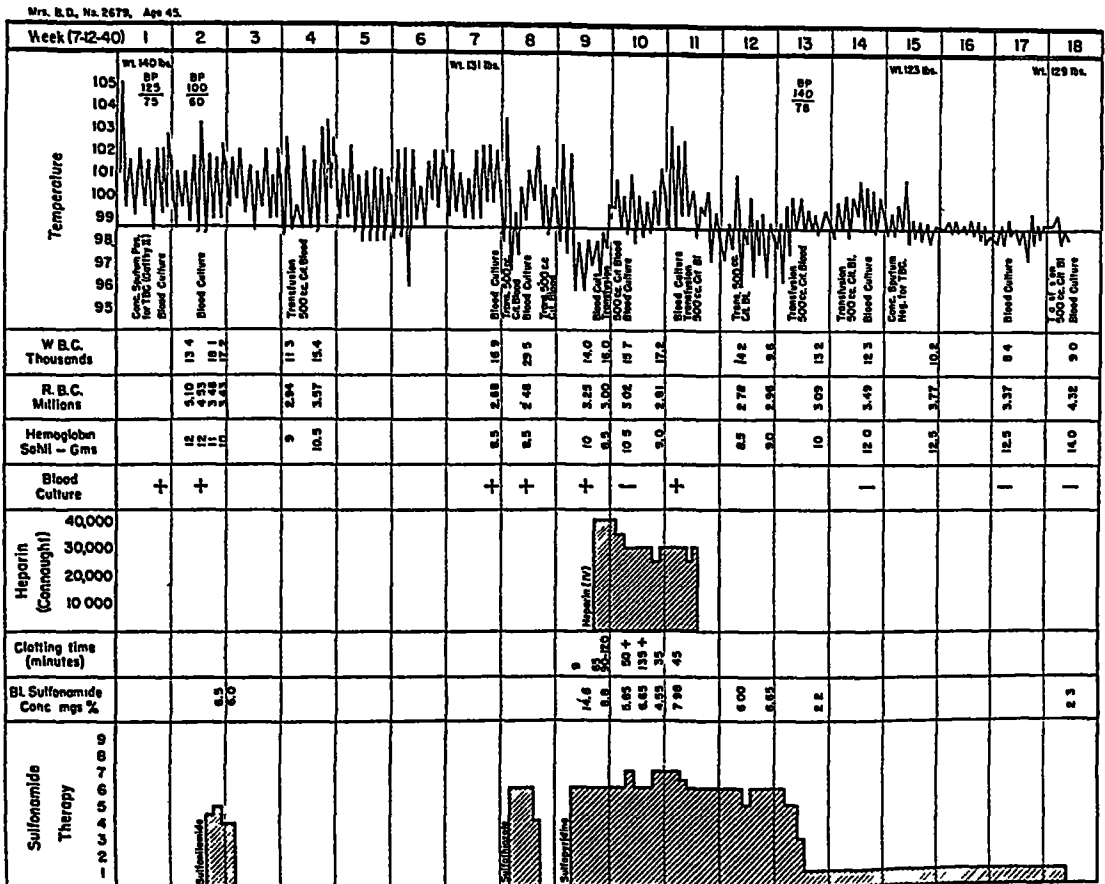


FIG 2

Correspondence with Dr Paul D White of the Massachusetts General Hospital, concerning the clinical history and course of this patient's illness, encouraged us to proceed with further active treatment. Influenced by the paper of Kelson and White,¹ we had sought this direct consultation and through the courtesy of Dr White were advised to combine sulfapyridine and heparin, using the method described in the paper by Kelson and White.

All medication except vitamins was stopped and sulfapyridine started at noon on September 7, 1940, on the fifty-seventh day of hospitalization. The dosage was regulated by blood concentration determinations. This was followed immediately by a drop to subnormal temperatures. The administration of intravenous heparin (Connaught) solution was started on the fourth day following the beginning of sulfapyridine, when a blood level concentration of 14.6 gm per cent had been reached. A fifth blood culture taken on September 10, 1940, showed one colony of *Streptococcus viridans* per 3 c.c. of blood (despite sulfonamide present in blood).

The blood clotting time previous to heparinization by the "5 tube method" was recorded as nine minutes

Heparin was added to either 10 per cent or 2½ per cent dextrose in normal saline, starting with 20,000 units (20 c.c.) to each liter flask of dextrose solution, and using two flasks (liters) per 24 hours, thereby administering 40,000 units of heparin for the first few 24 hour periods. This resulted in a rapid increase in the clotting time, which at first became excessive (90 to 120 minutes) and from then on the amount of heparin given was reduced and varied according to the clotting time (see figure 2). A clotting time of at least 45 minutes seemed desirable. Ascorbic acid was also given in daily doses of 150 mg by mouth.

The intravenous administration of heparin was continued for a period of two weeks without interruption. Sulfapyridine was continued in doses of 5 to 7 grams per 24 hours, for 26 days, and then decreased to a maintenance dose of one gram per 24 hours. This small dose was continued for two months after the patient left the hospital for a total administration time of slightly over three months. It was then voluntarily discontinued because the patient stated that it made her "short of breath."

Blood cultures were repeated at intervals, as shown in figure 2, and three negative cultures obtained before discharge from the hospital.

There was marked clinical improvement in the appearance of the patient on the third day following the beginning of heparinization. She talked and joked freely and developed a good appetite. Supportive transfusions were given (see figure 2). The basal systolic murmur became less intense, the spleen remained palpable. There was occasional chest pain beneath the right axilla. On September 24, 1940, the intravenous administration of heparin was stopped. At least 30,000 units per 24 hours had been necessary to keep the clotting time between 30 and 45 minutes. Shortly thereafter, a period of afternoon temperature elevation followed (see figure 2), accompanied by pain over the spleen (? infarct) and occasional nausea and vomiting. Some tenderness to palpation was present in the splenic area but this subsided in the next four to five days.

The patient continued to improve until September 29, 1940, the sixth day following cessation of heparin when, after eating luncheon, she suddenly broke out in cold perspiration and complained of marked cardiac palpitation, dyspnea, and precordial pain. The pulse rate at the apex and wrist was so rapid it could not be counted. She was given 1/120 gr of strophanthin intravenously and 1/32 of dilaudid subcutaneously. The pulse rate decreased to 160 beats per minute and four hours later she vomited and the cardiac irregularity ceased. Auricular premature beats were present for the next 24 hours and then disappeared.

Two weeks later the patient was well enough to have chair and blanket privileges. The blood pressure was 140 mm Hg systolic and 78 mm diastolic. The cardiac sounds were of fair quality and regular in rhythm. The systolic murmur was less intense over the mitral area and was still directed toward the base where it became a loud continuous cardiac murmur. No thrills were present. The diastolic murmur remained faint and was best heard following slight exercise. There was no cough, expectoration or chest pain.

Three weeks later the spleen was no longer palpable, and temperature, pulse, and respiration were essentially normal. She had gained six pounds in weight and looked like a new person. Blood cultures remained negative. The patient was again transfused and discharged home by automobile on November 21, 1940, after 124 days of hospitalization.

Following discharge she has returned periodically to the Out-Patient Department for follow-up observation. Sulfapyridine (1 gm per day) was stopped by the patient on January 13, 1941. A repeat blood culture on January 23, 1941 was negative for

bacterial growth. Blood studies on that day were as follows: Red blood cell count 5,350,000, hemoglobin 74 per cent (Sahli), white blood cell count 9,250. She had felt occasional slight irregularity of the heart beat. There had been no dyspnea on exertion, no edema, cough or chest pain. The blood pressure was 136 mm Hg systolic and 82 mm diastolic. A blood culture was repeated on April 2, 1941 and was again negative for growth. The cardiac murmurs remained unchanged. The last roentgenogram taken on June 27, 1941 (figure 3) revealed clearing in both bases with a few



FIG 3

persistent strands of organization on the right. There was little change in the size or shape of the heart which still appeared somewhat generally enlarged. The patient was in excellent health and spirits and was leading a quite normal and only slightly restricted life.

She was last examined on October 25, 1941 and had gained in weight to 188 pounds and appeared in good health. There had been occasional short periods of cardiac irregularity. No cough, chest pain, or edema was noted. There was no dyspnea on exertion. A roentgenogram revealed no important change in the appearance or size of the heart or within the lung fields since the previous film. An electrocardiogram was normal with no evidence of axis preponderance.

On October 30, 1941, the patient was seen by Dr. Paul D. White at Stanford University Hospital. He found no evidence of rheumatic valvular disease but made a diagnosis of patent ductus arteriosus*.

*The patient was last seen on September 23, 1942 and was in excellent health. The cardiac murmur persisted unchanged and a roentgenogram of the chest revealed well healed fibrosis in both bases of the lungs. The cardiac outline revealed slightly more prominence of the pulmonary conus.

DISCUSSION

In this case there were two infections, namely, the tuberculous one and bacterial endarteritis of alpha-hemolytic streptococcus type complicating a congenital cardiac defect (patent ductus arteriosus). Of the two separate disease processes the blood stream infection was the more important from the standpoint of preservation of life. This called for energetic treatment if a fatal outcome were to be averted. The pulmonary tuberculous infection was of secondary consequence.

In view of the successful outcome and apparent cure of the bacterial endarteritis in this case, further support is added to the idea advanced by Kelson and White in combining sulfapyridine and the anticoagulant effect of heparin in the treatment of this highly fatal disease. The pulmonary tuberculous infection was not unfavorably influenced by this therapy, to the contrary, it became quiescent as manifested by roentgenographic improvement and conversion of positive sputum.

The pulmonary pathologic changes must be considered as considerably complicated. The following elements enter the picture: namely, the passive vascular congestion of the lungs secondary to possible myocardial failure, the occurrence of septic pulmonary emboli, and the existence of a tuberculous infection manifested by acid-fast bacilli in concentrated sputum. It would be difficult to delineate one from the other by the pulmonary roentgenogram. It is conceivable that the tuberculous infection was a minor one, perhaps a "lighting up" of an old imperfectly healed pulmonary focus occurring as a result of the acute congestive and embolic pulmonary processes.

SUMMARY

Subacute bacterial endarteritis engrafted upon a patent ductus arteriosus and associated with a mild pulmonary tuberculous infection is reported in a woman of 45.

Treatment by sulfapyridine and the anticoagulant heparin in combination, according to the method of Kelson and White, resulted in sterilization of the blood stream and complete recovery from both the endarteritis and the tuberculous infection. Follow-up studies over a period of one year following discharge from the hospital are fully confirmative of the effectiveness of the therapy.

The authors wish to note their appreciation and indebtedness to Dr. Paul D. White for helpful criticism and advice, both in the treatment of the patient and in preparation of the paper.

BIBLIOGRAPHY

1. Kelson, S. R., and White, P. D. A new method of treatment of subacute bacterial endocarditis, *Jr Am Med Assoc*, 1939, cxiii, 1700.
2. Leach, C. E., Faulkner, J. M., et al. Chemotherapy and heparin in subacute bacterial endocarditis, *Jr Am Med Assoc*, 1941, cxvii, 1345.

EDITORIAL

POSSIBLE SUBSTITUTES FOR HUMAN PLASMA

THE need for huge quantities of human plasma in the treatment of war injuries has naturally stimulated the search for material from some foreign species of animal which would serve as a suitable substitute. It has been shown in human as well as animal experiments that serum or plasma of the horse or cow is effective in the treatment of shock in individuals who tolerate it. The risk of immediate serious reactions, however, as well as its property of sensitizing individuals to future injections, preclude the use of unaltered foreign serum or plasma.

Wangensteen and associates¹ have reported a study of the effect of injections of bovine serum or plasma in 120 human subjects, chiefly cases of inoperable carcinoma. Individuals giving a positive intracutaneous reaction to bovine serum were excluded for the most part, as they "did not take serum well." Three patients with negative intracutaneous tests, furthermore, suffered violent anaphylactic reactions, and over 60 per cent of the subjects had immediate reactions less severe in type. Two patients who were in shock, however, showed a rise in blood pressure after the injections, and metabolic studies in some cases were reported as indicating that some protein was retained and utilized.

Horse serum is less toxic than bovine serum, in animal experiments about one-fifth as toxic, but is still unsafe for therapeutic use.

Many efforts have been made to eliminate these reactions. For the most part these have sought either to separate the various proteins in plasma, usually by fractional precipitation, and discard the fractions which are most toxic and antigenic, or so to alter the protein molecule by physical or chemical means as to eliminate its specificity and antigenicity without actually destroying the molecule.

It has long been known that plasma albumin and plasma globulin are antigenically distinct, and that the globulin is much more highly antigenic than the albumin. That is, the minimal dose of serum albumin which will sensitize an animal, and also the minimal dose which will cause fatal shock in a sensitized animal, are much greater than the corresponding doses of globulin. Studies in animals indicate that the difference may be about 100 fold. Essentially the same ratio probably applies to man.

Janeway and Beeson,² who studied the effect of a purified bovine plasma albumin solution in dogs, mention its administration to 16 human cases without reactions. Davis, Eaton and Williamson³ also report administering

¹ KREMEN, A. J., HALL, H., KOSCHNITZKE, H. K., STEVENS, B., and WANGENSTEEN, O. H. Studies on the intravenous administration of whole bovine plasma and serum to man, *Surgery*, 1942, xi, 333-355.

² JANEWAY, C. A., and BEESON, P. B. The use of purified bovine albumin solutions as plasma substitutes, *Jr Clin Invest*, 1941, xx, 435 (abstract).

³ DAVIS, H. A., EATON, A. G., and WILLIAMSON, J. Transfusion of bovine serum albumin into human beings, *Proc Soc. Exper Biol and Med*, 1942, xlii, 96.

beef albumin solution to 13 human cases without reaction. Keys, Taylor and Savage⁴ state, however, that they have found no natural foreign protein fraction which does not cause reactions in some individuals. The albumin fraction caused the least reaction, although it sensitized readily to subsequent injections. A person sensitive to one species of foreign protein was often sensitive to other species but not necessarily to all. They found intracutaneous tests useful in selecting a suitable species of foreign protein solution for use in a given patient. Albumin solution restored animals shocked by bleeding, it remained in the circulation for days, and behaved physically like the individual's own protein.

Such observations indicate that the use of purified albumin solutions eliminates a large proportion of the reactions caused by whole serum or plasma, but not all of them, and that albumin sensitizes to subsequent injections of itself. Practically its use at present appears limited to emergencies when homologous plasma is not available, and to individuals giving a negative intracutaneous reaction.

Quantitative studies in animal experiments support this conclusion that natural albumin solutions are too highly antigenic for safe general use. The early studies of Doerr and Russ and of Wells on guinea pigs, as well as those of later observers, showed that the minimal sensitizing dose of horse serum is about 0.00001 c c, and the minimal (intravenous) shocking dose, 0.01 c c, although smaller amounts cause milder reactions. Normal human beings are much less sensitive than guinea pigs, but those persons who are spontaneously allergic may be extremely hypersensitive. Death has been reported after the intradermal injection of one-twentieth of a c c of horse serum. To be reasonably safe for sensitive persons, it would seem necessary that the antigenic activity of the material in a liter of protein solution should not exceed that of 0.01 c c or at most 0.1 c c of normal horse serum. This would be a reduction of 100,000 fold. Since the substitution of albumin for whole serum accomplishes only about a 100 fold reduction, some means of altering the protein must be sought. A suitable procedure must accomplish two objectives. It must reduce the capacity of the material to cause shock in animals sensitive to whole serum, a deviation of specificity, or "despeciation", and it must reduce the ability of the treated protein to sensitize normal animals against itself, a destruction of all its antigenic properties.

Some degree of loss of antigenicity has been obtained by the use of heat, and in greater degree by acidification or alkalization, and by controlled peptic digestion. Coghill and associates⁵ used taka diastase in order to reduce the shocking power of the horse serum in diphtheria antitoxin. At the expense of about half of its antitoxin content, they obtained a product

⁴ KEYS, A., TAYLOR, H. L., and SAVAGE, G. Utility of animal blood in preparation of plasma for transfusion, *Jr Am Med Assoc*, 1941, cxvii, 62.

⁵ COGHILL, R. D., FELL, N., CREIGHTON, M., and BROWN, G. The elimination of horse-serum specificity from antitoxins, *Jr Immunol*, 1940, xxxix, 207-222.

whose power to shock guinea pigs sensitized to normal horse serum was reduced to about one three-hundred-and-twentieth of the original. He was unable to cause fatal shock with any dose which was not fatal to the control animals, and stated that these results were being largely confirmed by studies in man.

Smetana and Shemin⁶ showed that photo-oxidation in the presence of hematopoiphyrin destroyed the antibodies in certain immune sera and destroyed the antigenic properties of egg albumin. Special studies indicated that the protein molecules were altered rather than disintegrated.

Henry⁷ has recently reported using this procedure in an attempt to alter the antigenicity of normal horse serum. The best results were obtained by exposing thin layers of serum to ultraviolet light in the presence of hematoporphyrin for a 96 hour period. He then studied quantitatively the capacity of the oxidized serum to stimulate precipitin formation in rabbits, to sensitize guinea pigs, and to intoxicate guinea pigs sensitized to horse serum. It was easier to secure a deviation in specificity than a loss of all antigenic activity. However, the active antigenicity of the treated serum was only about one ten-thousandth of the original. The residual material which retained the antigenicity of the original horse serum was the equivalent of 0.01 c c per liter. These figures closely approximate those which theoretically are the maximum consistent with reasonable safety for use in man. Thus far, however, no reports have appeared as to the actual toxicity or therapeutic efficacy of the treated serum in human experiments. Possibly the application of this procedure to the albumin fraction of horse serum might yield a safer product than that obtained from whole serum.

Chemical study of the oxidized serum showed that tryptophane had been removed from the molecule. The greater part of the original protein, however, was still precipitable by the usual reagents. Studies by means of electrophoresis and ultracentrifugalization indicated a polydispersion of the protein, that is, a marked variation in the size of the different protein molecules with the presence of large aggregates two to three times the size of the original molecules. It seems probable, therefore, that there had been an alteration rather than an actual break down of the molecules. If tests in man show that the antigenicity has been sufficiently reduced, it may be hoped that the protein in the treated serum will remain in the circulation and adequately replace homologous plasma in the emergency treatment of shock.

There are as yet no adequate observations to show to what extent such foreign protein can participate in satisfying the nutritional needs of the body. The importance of this function of the plasma proteins has been emphasized by Whipple and has been previously discussed here.⁸ Earlier

⁶ SMETANA, H., and SHEMIN, D. Studies on photo-oxidation of antigen and antibodies, *Jr Exper Med*, 1941, lxxiii, 223-242.

⁷ HENRY, J. P. Quantitative studies of the photochemical despeciation of horse serum, *Jr Exper Med*, 1942, lxxvi, 451-476.

⁸ Editorial. Plasma proteins, *ANN INT MED*, 1940, xiv, 533.

work of Holman, Mahoney and Whipple⁹ indicated that in dogs homologous plasma protein was retained and utilized but foreign plasma (unaltered) was not. Recent observations of Elman and Davey¹⁰ in dogs cast doubt on their ability freely to utilize even homologous plasma protein administered intravenously. If the altered foreign protein cannot be utilized effectively in nutrition, its value would be distinctly limited. The experiments already reported, however, warrant the hope that a procedure will be perfected which will render foreign serum safe from the standpoint of immediate reactions and suitable at least for use in emergencies.

⁹ HOLMAN, R. L., MAHONEY, E. B., and WHIPPLE, G. H. Blood plasma protein given by vein utilized in body metabolism, dynamic equilibrium between plasma and tissue proteins, Jr. *Exper. Med.*, 1934, *lii*, 269-282.

¹⁰ ELMAN, R., and DAVLY, H. W. Studies on hypoalbuminemia produced by protein-deficient diets. III. The correction of hypoalbuminemia in dogs by means of large plasma transfusions, Jr. *Exper. Med.*, 1943, *lxvii*, 1-5.

REVIEWS

Formulary and Handbook of The Johns Hopkins Hospital Edited by JOHN C KRANTZ, JR 253 pages, 11 5 × 17 5 cm John D Lucas Co, Baltimore 1942 Price, \$2 00

The material in this book was originally compiled by members of the staff representing the various departments of the Johns Hopkins Hospital, primarily for the guidance of interns and residents in prescribing drugs and other therapeutic measures. In effect it is an abbreviated pharmacopeia and formulary, including only those drugs and mixtures which are regarded as important and which are actually in general use in the wards and dispensary in each of the principal departments of the Hospital. The number of preparations considered is therefore limited to a relatively small group which have survived a long period of natural selection.

Each preparation is described, indications for its use are stated, as well as dose and directions for administration. In separate sections are included special drugs and mixtures used in the departments of urology, gynecology, dermatology, ophthalmology, and laryngology. Vitamins, endocrine preparations and biological products are included, as well as diagnostic agents. Directions are given for a few special therapeutic procedures such as transfusion. There is also a short section giving treatment of the commoner types of poisoning.

The book contains a surprising amount of useful information, easily available, and "ballast" has been almost entirely eliminated. It is not designed as a textbook, but will be very useful for the purpose for which it was intended.

P W C

Fever Therapy Technique By JACK R EWALT, M D ERNEST H PARSONS, M D, STAFFORD L WARREN, M D, and STAFFORD L OSBORNE, M D 161 pages 13 × 19 cm Paul B Hoeber, Inc, New York 1939 Price, \$2 50

This book of 154 pages of text contains a concise, lucid exposition of the various methods of inducing fever for therapeutic purposes. In only one respect do I take exception to the views of the authors. This is in their criticism of those who object to the "one day fever plus chemotherapy" scheme of treatment of syphilis. The authors may recall that this form of therapy has been used in Europe with poor results in that numerous relapses have occurred. Although it is desirable that methods designed to hasten a cure should be investigated, the results thus far obtained do not warrant criticism if we advise patients against too great an enthusiasm for this form of treatment at the present time.

On the whole this book is a desirable compend for the physician who expects to use fever therapy.

H M R

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Hospital Care of the Surgical Patient By GEORGE CRILE, JR, M D, and FRANKLIN L SHIVELY, JR, M D With a Foreword by Evarts A Graham, M D 184 pages, 22 × 14 5 cm 1943 Charles C Thomas, Springfield, Illinois Price, \$2 50

What the Citizen Should Know about Wartime Medicine By JOSEPH R DARNALI, M D, Lieutenant Colonel, Medical Corps, United States Army and V I COOPER

237 pages; 21 × 14 cm 1942. W. W. Norton & Company, Inc., New York
Price, \$2 50.

Mind Perception and Thought in Their Constructive Aspects. By PAUL SCHILDER
432 pages, 22 × 14 5 cm. 1942 Columbia University Press, New York Price,
\$5 00

Goals and Desires of Man. By PAUL SCHILDER 305 pages, 22 × 14 5 cm 1942
Columbia University Press, New York. Price, \$4 00

Mental Health in College By CLEMENTS C FRY, M.D., WITH THE COLLABORATION OF
EDNA G ROSTOW 363 pages, 23 5 × 16 cm 1942 The Commonwealth Fund,
New York Price, \$2 00

The Hemorrhagic Diseases and the Physiology of Hemostasis By ARMAND J. QUICK,
PH D, M D 340 pages, 25 × 16 cm 1942 Charles C Thomas, Springfield,
Illinois Price, \$5 00

Infant and Child in the Culture of Today By ARNOLD GESELL, M D, and FRANCES
L ILG, M D, IN COLLABORATION WITH JANET LEARNED, M A, and LOUISE B
AMES, PH D 399 pages, 26 × 19 5 cm 1943. Harper & Brothers, New York
Price, \$4 00

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,122 Fellows and Associates of the College on active military duty. Herewith are reported the names of 96 additional members, bringing the grand total to 1,218.

Ladislaus L. Adamkiewicz
Frank W. Anzinger
Karl F. Arndt

Justus M. Barnes
Lawrence H. Beizer
Joseph E. Brackley
Henry A. Bradford
Edward S. Brewster
Hildahl I. Burtness
Otto L. Burton

John R. Cavanagh
Augustus H. Clagett, Jr.
H. Dick Countryman
J. Antrim Crellin
George R. Crisler

Constance A. D'Alonzo
Joseph H. Delaney
Albert H. Douglas
Joseph L. Duffy
J. Richard Durham

Joseph C. Ehrlich
Ephraim P. Engleman
William D. Evans

I. Donald Fagin
Isidore A. Feder
Lester C. Feener
Frederick W. Fitz
Frank P. Foster

John L. Gompertz
Edgar S. Gordon
Clark C. Goss

Frederic W. Hall
Mason V. Hargett
Robert M. Harris
Harold E. Hathhorn
Carl C. Hoffman, II
Ellis H. Hudson
Samuel Hurwitz

Thomas C. Jaleski
Frederick A. Johansen
Frank T. Joyce

Clyde H. Kelchner
Ernest Q. King
Roy E. Kinsey
Carl J. Kornreich
Alfred L. Kruger

Byrd S. Leavell
Harris V. Lilga
Louis S. Lipschutz
Joseph H. Low
Clayton J. Lundy
Charles H. Lutterloh

Frank R. Maddison
Robert C. Manchester
Edward A. Marshall
Walter P. Martin
Thomas C. McCleave, Jr.
James W. McElroy
Frank B. McGlone
Samuel Melamed
William C. Menninger
William C. Meredith
Saul Michalover
Laurence C. Milstead
Norman L. Murray

Robert A. Newburger

J. Frederick Painton
Harry Parks
J. Winthrop Pennock
Thornton T. Perry, III

George N. Raines
Earl B. Ray
H. Walden Retan
Abraham I. Rosenstein
Oscar F. Rosenow

Earl Saxe
Walter L. Schafer

Israel A Schiller
 Louis A Schwartz
 Solomon Silver
 Elmer R Smith
 Saul L Solomon

 Gordon B Tayloe
 Kent H Thayer
 Morris C Thomas
 Arthur M Tunick
 Kilby P Turrentine

Colman R Tyler

 Wesley Van Camp

 Richard Wagner
 Levi M Walker
 Lorenz M Waller
 Bernard A Watson
 Fitz-John Weddell, Jr
 Lee Williamson
 Willis D Wright

In the News Notes section of the January, 1943, issue of this journal we reported the election of 147 Fellows and 140 Associates. With these additions and with other adjustments made in the College membership at the meeting of the Board of Regents, December 13, 1942, such as reinstatements and deletions due to the expirations of the maximum five-year Associate term, the total membership of the College now is as follows

4 Masters
 3,844 Fellows
 1,118 Associates

 4,966

NEW LIFE MEMBER

Dr Charles Leonard Hess, F A C P, Bay City, Mich, became a Life Member of the American College of Physicians on January 5, 1943

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

Dr Charles J Bloom, F A C P, New Orleans, La—"The Care and Feeding of Babies in Warm Climates",
 Dr Henry A Christian, F A C P, Brookline, Mass—"Osler's Principles and Practice of Medicine," 14th edition

Reprints

Dr Alvan L Barach, F A C P, New York, N Y—51 reprints,
 Dr Edward W Cannady, F A C P, East St Louis, Ill—1 reprint,
 Dr. O P J Falk, F A C P, St Louis, Mo—1 reprint,
 Dr Hyman I Goldstein (Associate), Camden, N J—2 reprints,
 Jerome S Levy (Associate), Captain, (MC), U S Army—2 reprints,
 Horace P Marvin, F A C P, Lieutenant Colonel, (MC), U S Army—1 reprint,
 Dr Ralph M Tandowsky, F A C P, Los Angeles, Calif—2 reprints

The Reading Hospital Reading, Pa, contributed a copy of the "History of the Reading Hospital, 1867-1942" to the College Library This History was published by the Board of Managers of the Hospital on the occasion of its 75th anniversary, December 9, 1942

Colonel Otis O Benson, (MC), U S A (Associate), is Chief of the Aero Medical Laboratory, Engineering Division, that has been recently built and equipped at the Army Air Forces Materiel Center, Wright Field, Dayton, Ohio

"Physiology of Flight—Human Factors in the Operation of Military Aircraft" is the title of a book containing a compendium of lectures and demonstrations given to the Army Air Force personnel, and prepared by the Aero Medical Research Laboratory under Colonel Benson Information is being simplified by illustrating it in the best "Popular Mechanics" manner, and will be published as a Technical Order for all flying personnel to read Colonel Benson has contributed a copy of this publication to the College Library

MANPOWER COMMISSION AND MEDICAL CARE FOR CIVILIANS

Mr Paul V McNutt, Chairman of the War Manpower Commission, on January 10 made the announcement that every effort to furnish adequate medical care for civilians would be made His statement was based on a report by Dr Frank H Lahey, Chairman of the Directing Board, Procurement and Assignment Service for Physicians, Dentists and Veterinarians

Some physicians, Dr Lahey indicated, will be asked to volunteer for practice in areas other than those in which they are now located This will be done to assure at least a minimum standard of medical care It is hoped that in most instances relocation of a physician can be accomplished within the States in which he is now licensed To obtain greater mobility of physicians, it is pointed out that some method of temporary licensing for the duration will probably have to be arranged in some States More than 400 physicians have already been relocated The names of other physicians who are willing to be and who can be relocated are being submitted to the Procurement and Assignment Service The U S Public Health Service and the Procurement and Assignment Service are making careful studies of industrial and other critical areas where relatively large numbers of physicians will be needed In estimating the availability of physicians for civilian or military service, certain adjustments are made for (1) lessened effectiveness of those over 65, (2) number of physicians giving full time service in certain Governmental and private agencies, (3) numbers now acting as residents and house officers

The total number of American physicians is approximately 180,000 It is estimated that the medical needs of the Armed Forces in 1943 can be met with an additional 10,000 physicians, and there will be left more than 80,000 active civilian physicians, estimated as sufficient to care for the needs of the civilian population if properly distributed and allocated, and if civilians will take every possible health precaution to keep well

Recruiting in 1943 will be confined to States with a disproportionately large number of physicians At the present time the following States show shortages of physicians Alabama, Arizona, Arkansas, Colorado, Georgia, Idaho, Kentucky, Louisiana, Mississippi, New Mexico, North Carolina, South Carolina, South Dakota, Tennessee and West Virginia

A C P POSTGRADUATE COURSES

The 1943 Bulletin of Postgraduate Courses was distributed to all members of the College in late December The Program for 1943 was greatly reduced, there being

only three courses, all in Internal Medicine No 1, University of Minnesota Center for Continuation Study, January 25-30, No 2, The Mayo Foundation, University of Minnesota, and The Mayo Clinic, February 1-6, No 3, Boston University School of Medicine, Massachusetts Memorial Hospitals, April 5-10

Courses 1 and 2 were closely coordinated, with the result that most of the registrants took both courses. The registration for these two courses, now completed, exceeded all expectations of the Advisory Committee on Postgraduate Courses. Physicians were in attendance from all parts of the United States and Canada, and the signal success of these courses proved conclusively that such opportunities are definitely in demand during the War.

Course 3 at the Boston University School of Medicine, under the direction of Dr Chester S. Keefer, F A C P, April 5-10, also has a gratifying registration. There is still time to register, but the maximum number that can be accommodated is nearly reached.

The 5th Annual Congress on Industrial Health, sponsored by the Council on Industrial Health of the American Medical Association, was held in Chicago, Ill., January 11-13, 1943. Among those who participated in the program were

- Dr John H. Foulger, F A C P, Wilmington, Del—"Preventive Medicine in Industry",
- Dr Chester S. Keefer, F A C P, Boston, Mass—"Respiratory Infections in Industry. Joint Report Prepared by the Council on Pharmacy and Chemistry and the Council on Industrial Health, American Medical Association",
- Dr James P. Leake, F A C P, Bethesda, Md—"Vaccines and Serums. Indications and Procedure",
- Dr Lemuel C. McGee, F A C P, Wilmington, Del—"Occupational Disease in Munitions Workers",
- Dr Anton J. Carlson, F A C P, Chicago, Ill—"The Older Worker",
- Dr Raymond Hussey, F A C P, Baltimore, Md—"Report of the Committee on Workmen's Compensation of the Council on Industrial Health"

Thomas F. Duhigg, F A C P, Commander, (MC), U S Navy, has been elected President of the Society of Ex-Resident and Resident Physicians of the Philadelphia General Hospital.

Dr Andrew L. Banyai (Associate), Wauwatosa, Wis., spoke on "Non-tuberculous Pulmonary Infections" at a meeting of the West Allis Medical Society, West Allis, Wis., December 3, 1942.

Dr John C. White, F A C P, New Britain, Conn., has been appointed Superintendent of the New Britain General Hospital.

Arthur P. Hitchens, F A C P, Lieutenant Colonel, (MC), U S Army, was one of the speakers at the meeting of the Medical Society of the District of Columbia, November 18, 1942. This meeting was devoted to a panel discussion on "Undulant Fever, Brucellosis and Bang's Disease."

Dr Francis E. Harrington, F A C P, Minneapolis, Minn., was recently appointed Director of the Minneapolis General Hospital.

Lloyd R Newhouser, F.A.C.P., Commander, (MC), U S Navy, spoke on "Treatment of Shock, Including Use of Blood Plasma" at the annual combined medical-dental meeting of the organized medical and dental professions of Greater New York, December 7, 1942

Dr Howard K Petry, F.A.C.P., Harrisburg, Pa, spoke on "Shock Treatment of Psychoses" at a recent meeting of the Dauphin (Pa) County Medical Society in Harrisburg

The Medical Society of Milwaukee (Wis) County sponsored a series of three lectures on the gastro-intestinal tract, November 2-4, 1942 Dr Walter C Alvarez, F.A.C.P., Rochester, Minn, discussed "Functional Disorders", Dr J Edwin Habbe, F.A.C.P., Milwaukee, discussed "Neoplasms", and Dr William M Jermain, F.A.C.P., Milwaukee, discussed "Inflammatory Disorders"

The President of the United States has renominated Ross T McIntire, F.A.C.P., Rear Admiral, (MC), U S Navy, to be Chief of the Bureau of Medicine and Surgery of the U S Navy Admiral McIntire has been a member of the Medical Corps of the U S Navy since 1917 and was first appointed Surgeon General of the Navy in 1938

Dr Moses Barron, F.A.C.P., Minneapolis, Minn, spoke on the "Medical Management of Peptic Ulcer" at a meeting of the Minnesota Academy of Medicine in St Paul, October 14, 1942

Dr Lloyd F Craver, F.A.C.P., New York, N Y, discussed "Cancer and Allied Disorders" at a meeting of the Dauphin (Pa) County Medical Society in Harrisburg, December 1, 1942

At the recent meeting of the American Public Health Association in St Louis, Mo, Dr Felix J Underwood, F.A.C.P., Jackson, Miss, was named President-Elect

On November 13, 1942, Philip S Hensch, F.A.C.P., Lieutenant Colonel, (MC), U S Army, addressed the El Paso (Colo) County Medical Society at Camp Carson Base Hospital Colonel Hensch spoke on "Management of Chronic Arthritis"

At a meeting of the Medical Society of the District of Columbia, December 9, 1942, commemorating its 125th anniversary, Dr Arthur C Christie, F.A.C.P., Washington, D C, a Past President of the Society, spoke on "Medicine in the Nation's Capital, 1817-1942"

At a midwinter scientific session of the Central States Society of Industrial Medicine and Surgery held in Chicago, Ill, December 11, 1942, Dr Italo F Volini, F.A.C.P., Chicago, spoke on "Sulfon Drug Therapy"

Dr Louis N Katz, F.A.C.P., Chicago, Ill, spoke on "The Diagnostic Value of the Electrocardiogram Based on an Analysis of 149 Autopsied Cases," and Dr George E Wakerlin, F.A.C.P., Chicago, Ill, spoke on "Treatment of Experimental

Renal Hypertension" at a joint meeting of the Chicago Society of Internal Medicine and the Clinical Section of the Chicago Heart Association

Students and members of the faculty at Cornell University, Ithaca, N Y, recently cooperated in a two-week experiment to test new vaccines. The experiment was under the direction of the Army Influenza Commission and was directed by Dr Norman Plummer, F A C P, and Dr Herbert K. Ensforth (Associate), both of New York, N Y

Dr Charles E. Lyght, F A C P, Professor of Health and Physical Education for Men and Director of the Carleton College Health Service, Northfield, Minn., has been appointed Director of Health Education of the National Tuberculosis Association

Dr Raymond Hussey, F A C P, Baltimore, Md., has been named a member of the Medical Committee of the Industrial Hygiene Foundation

Edward R. Stitt, F A C P, Rear Admiral, Retired, (MC), U S Navy, was one of three military physicians who was presented with the first awards of the newly established Gorgas Medal. Admiral Stitt was cited "for extensive research and writing on tropical maladies and their prevention"

These awards were recently established by John Wyeth and Brother, Inc., Philadelphia, Pa., in memory of Surgeon General William Gorgas, whose work in preventive medicine made it possible to construct the Panama Canal. The awards include silver medals inscribed with the likeness of General Gorgas and a cash award of \$500.00

Dr Israel M. Rabinowitch, F A C P, Associate Professor of Medicine, McGill University Faculty of Medicine, Montreal, Quebec, conducted a course of lectures and demonstrations on "Chemical Warfare," October 19-30, 1942, sponsored by McGill University Faculty of Medicine under the auspices of the Director of Civil Air Raid Precautions

At the annual meeting of the Institute of Medicine of Chicago, December 10, 1942, Dr George H. Coleman, F A C P, was named Secretary and Dr Grant H. Laing, F A C P, Treasurer

On December 16, 1942, the Polk (Iowa) County Medical Society conducted a panel discussion on "The Sulfonamides." The discussion was under the direction of Dr Daniel J. Glomset, F A C P, Des Moines, Iowa

Dr Arthur F. Chace, F A C P, New York, N Y, was elected President of the New York Academy of Medicine, December 3, 1942, to serve for a two-year term. Dr Cornelius P. Rhoads, F A C P, New York, N Y, was elected a Vice President of the Academy to serve for a three-year term

At the 62nd Annual Dinner of the Associated Alumni of the College of the City of New York, November 14, 1942, Dr Alvan L. Barach, F A C P, New York, N Y,

was awarded one of the Townsend Harris Medals in recognition of "notable post-graduate attainments"

On March 10, 1943, Dr Cornelius P Rhoads, F A C P, New York, N Y, will address a special meeting of the College of Physicians of Philadelphia Dr Rhoads will speak on "Newer Advances in Cancer Research"

Dr William E Robertson, F A C P, Philadelphia, Pa, was one of the physicians honored for having completed fifty years or more in the practice of medicine by the Philadelphia County Medical Society at a luncheon meeting, January 12, 1943

At a meeting of the North Texas District Medical Association held in Dallas, Tex, November 30, 1942, Dr Chester M Jones, F A C P, Boston, Mass, spoke on "Clinical Problems in Hepatic Disease" and Dr James H Means, F A C P, Boston, Mass, on "Diseases Affecting the Portal Circulation"

On December 18, 1942, the University of Texas Medical Branch, Galveston, conducted a special war program at its semicentennial graduation exercises Among the speakers were

- Dr Cyrus C Stungis, F A C P, Ann Arbor, Mich—"Blood and Substitutes in Shock",
 - Dr Franklin G Ebaugh, F A C P, Denver, Colo—"Psychiatry and War",
 - Dr Anton J Carlson, F A C P, Chicago Ill—"Obstacles in the Path of an Optimum Diet"
-

The 5th Annual Forum on Allergy was held in Cleveland, Ohio, January 9-10, 1943 Study groups were conducted by the following members of the College

- Dr Theodore L Squier, F A C P, Milwaukee, Wis—"Allergic Manifestations in the Blood",
- Dr John P Henry, F A C P, Memphis, Tenn—"Allergic Headaches",
- Dr Herbert J Rinkel, F A C P, Kansas City, Mo—"Food Allergy",
- Dr J Warrick Thomas, F A C P, Cleveland, Ohio—"Allergy of the Eye and Conjunctiva",
- Dr Karl D Figley, F A C P, Toledo, Ohio—"Vasomotor Rhinitis in Children",
- Dr Ralph Bowen, F A C P, Houston, Tex—"The Prevention of Allergy in Children",
- Dr Samuel M Fernberg F A C P, Chicago, Ill—"Asthma in Patients Over Forty-Five Years of Age",
- Dr Homer E Prince, F A C P, Houston Tex—"Allergy to Fungi",
- Dr George L Waldbott, F A C P, Detroit, Mich—"Industrial Allergic Dermatitis"

Dr Milton B Cohen F A C P, Cleveland, delivered a special lecture on "The Dynamic Mechanism of the Allergic Reaction" and Dr Roy W Scott, F A C P, Cleveland, on "Cardiac Asthma and the Heart in Asthma"

• Dr Elmer E Glenn, F A C P, Springfield Mo, was recently named President of the Missouri Tuberculosis Association

Dr. Charles H Neilson, F A C P., St Louis, Mo , has been chosen Vice President of the Missouri State Board of Health

A series of lectures on legal medicine are being conducted Friday evenings by the Office of the Coroner of Philadelphia (Pa) County, January 8-March 12, 1943 Among the local speakers were

January 8, 1943—Dr Edward B Krumbhaar, F A C P —“Causes of Sudden Death”,

January 29, 1943—Dr Edward A Strecher, F A C P —“Suicide ”

At a meeting of the Allegheny (Pa) County Medical Society in Pittsburgh, December 15, 1942, Dr Joseph T Beardwood, Jr , F A C P , Philadelphia, spoke on “Management of Diabetic Emergencies” and Dr Angelo L Luchi (Associate), Wilkes-Barre, on “Diabetic Diets and Food Habits of the Nationalities ”

Dr Chester N Frazier, F.A C P , has been appointed Professor of Dermatology and Syphilology at the University of Texas Medical Branch in Galveston Dr Frazier was recently engaged in venereal disease control work at the Johns Hopkins School of Hygiene and Public Health, Baltimore, Md

Dr Frank Krusen, F A C P , Rochester, Minn , officially represented the American College of Physicians recently when the Army-Navy “E” Production Award was made to H G Fisher & Co, Chicago Dr John S Coulter represented the American Medical Association, Dr Bowman C Crowell, the American College of Surgeons and Dr W P Morrell, the American Hospital Association The Governor of the State of Illinois was represented by Major General Frank Parker, formerly Commander of the First Division in France, who made an address Honorable Edward J Kelly, Mayor of the City of Chicago, also made an address The Award was made by Rear Admiral K C Melhorn (MC), U S N (F A C P), and the pins were awarded by Lieutenant Colonel M E Griffin, (MC), U S A The Navy provided a color guard and a twenty-eight piece band The ceremony was inspiring and was attended by many men of prominence

The Medical and Surgical Relief Committee of America reports receipt of seventy-six cartons containing about five thousand pounds of surgical instruments rescued from scrap metal collections They were donated by Dr Walter L Bierring, F A C P , State Health Commissioner of Iowa, when it was learned that many of the instruments contributed to the recent Iowa scrap metal campaign were in good condition and would more effectively serve the war effort if reconditioned and made available to the various organizations which call on the Committee for help After necessary repairs have been made, the instruments will be placed in emergency medical field sets for distribution to the U S Coast Guard, and to first aid posts, needy hospitals and other recognized relief agencies in the United States and Alaska

SPECIAL NOTICES

ANNOUNCEMENT

THE AMERICAN BOARD OF INTERNAL MEDICINE

Pursuant to the policy of the American Board of Internal Medicine to keep fees at a minimum consistent with efficient function of the Board it is now possible to

reduce the registration and examination fee. Accordingly, the following action has been directed. The registration and examination fee will be reduced from forty dollars to thirty dollars. The certificate fee will remain at ten dollars, making a total of forty dollars. The oral examination fee in the sub-specialties will remain at ten dollars.

This reduction in fees will become effective as of January 1, 1943, and will apply to candidates for the written examination on February 15, 1943 whose applications have not been accepted for a previous examination.

ERNEST E. IRONS, M.D.,
Chairman

CLEVELAND HEALTH MUSEUM

On the eve of its second anniversary civic luncheon November 20, 1942, Cleveland Health Museum received its first truck loads of exhibit material presented for the duration by the American Museum of Health, New York City. These accessions were selected from the Oberlaender Trust Collection and others displayed in the Hall of Man and Medicine at the New York World's Fair.

The exhibits chosen include such famous pieces as the muscle man, the nerve man, a body book of 16 pages, the nodding head, swinging ear, and acting heart. Models of cell development demonstrate marvels of heredity. More than 300 exhibit items show what is needed to keep the body running, what hazards threaten its existence, and what limitations must be considered affecting its use.

Most widely known is the Transparent Man whose outer form is modeled after the fourth century Greek statue of "The Praying Boy" which was once in the possession of Frederick the Great of Prussia. This exhibit, symbolic of the others which will be given special showings at the Museum in the beginning of 1943, was unveiled by Mrs. Elizabeth S. Prentiss whose support has helped immeasurably to sustain the Museum.

W. W. Peter, M.D., Dr. P. H., associate professor of public health, Yale University, spoke on "Keep the Health Fires Burning." He told how poor health is reducing manpower in this country. One out of five people in the productive age group (20 to 64 years old) are handicapped by chronic diseases, serious mental or physical illness. "Every state and city has its share of these unproductive people," Dr. Peter said. "It is important to mention them because your Museum here and all other contributing agencies can do something to improve conditions."

Bruno Gebhard, M.D., director of Cleveland Health Museum, who has been instrumental in the designing of New York World's Fair's health exhibits, came to Cleveland in 1940, to design and install exhibit material for its opening and to operate the Museum.

Since its opening, November 13, 1940, it has been visited by more than 66,000 people.

But its influence has been far more widespread than these statements indicate. The attendance figures include people who came from 44 states and several foreign countries, to take the message of Cleveland Health Museum back with them. By means of travelling exhibits the Museum has gone far beyond the territorial limits. It is estimated that more than a half million people from Boston and Bridgeport, to Huron, South Dakota and Huston, Texas, have seen the Museum's dramatic presentations of health facts.

OBITUARIES

DR SHERMAN GRANT BONNEY

Following a brief illness, Sherman Grant Bonney, F A C P, died in Denver on November 19, 1942. Dr. Bonney was born in Cornish, Maine, in 1864, the son of Dr. and Mrs. Calvin Fairbanks Bonney. In 1886, he received his A B degree at Bates College, Lewiston, Maine, in 1889, he received his M A degree from the same institution. In 1889, he received the degree of M D from Harvard Medical School.

After practicing for a brief period of time in Lewiston, Maine, where he married Miss Nancy B. Little, he came to Denver in 1890, and was in the active practice of medicine in this city until he retired in 1930.

During the course of a very long and active professional life, Dr. Bonney was Professor of Medicine and Dean of the Medical Department at Denver University, and Trustee and President of the Gross Medical College of Denver. At the time of the amalgamation of Colorado medical institutions, about 1910, Dr. Bonney was made Professor of Medicine, Emeritus, of the University of Colorado School of Medicine.

In 1908, he married Mrs. Jessie Ellwood Ray who survives him. In 1908, he published a textbook on tuberculosis, "Pulmonary Tuberculosis and Its Complications." This book, a pioneer in its field, embodied the experience of an enormous practice in tuberculosis, and brilliantly recorded the observations of a very keen mind. The second edition of this work appeared in 1910. In memory of his parents, he presented a public library to Cornish, Maine.

He was a member of the Medical Society of the City and County of Denver, the Colorado State Medical Society, the Denver Clinical and Pathological Society, a Fellow of the American College of Physicians, a Fellow of the American Medical Association, a member of the American Clinical and Climatological Association, the National Tuberculosis Association and the American Society for Tropical Medicine.

During the period of great popularity of Colorado as a health resort for tuberculous patients, Dr. Bonney enjoyed a great reputation. His practice at this time was enormous. He combined great diagnostic skill with a native shrewdness of judgment of human nature and a dogged determination to get his patient well. His retirement in 1930 was due solely to a failure of hearing. His health remained good up to the past year. His mental faculties, always very keen, were unimpaired up to the last.

JAMES J. WARING, M D, F A C P,
Governor for Colorado

DR FREDERICK FRETAGEOT GUNDRUM

Dr Frederick Fretageot Gundrum of Sacramento, California, one of our prominent physicians of northern California and a Fellow of the American College of Physicians since 1919, died on October 23, 1942

Dr Gundrum was born at New Harmony, Indiana, November 3, 1880. He graduated from the academic department of Stanford University in 1903 and from the Johns Hopkins University School of Medicine in 1908. He served an internship at the Johns Hopkins Hospital 1908 to 1909 and a residency at the St Francis Hospital, Pittsburgh, Pennsylvania, from 1909 to 1910. He was also Demonstrator in Anatomy at the Pittsburgh School of Medicine from 1909 to 1910. From 1912 to 1915 he was Director of the Northern Branch of the California State Hygienic Laboratory, and later Vice-President of the California State Board of Health, serving for several years. He served as a Member of the Staff of the Sacramento County Hospital for several years and was also Secretary and Member of the Board of Directors of Sutter Hospital, in Sacramento. In 1937 he was President of the San Francisco Academy of Medicine. He was a member of the California State Medical Society, Fellow of the American Medical Association, member of the American Public Health Association, and Diplomate of the American Board of Internal Medicine. He was the author of many published papers and for many years was a regular attendant and active participant in the annual meetings of the California State Medical Society.

Dr Gundrum was long a prominent physician in California and wielded an important influence in his community. His work in the Public Health field, which was an ancillary interest, was an important contribution to the State of California as he was one of the pioneers in this field and possessed the vision and administrative ability necessary for constructive effort.

He married Elizabeth Adams, September 3, 1913. She and two children, Elizabeth Eloise, and Frederick, Junior, survive.

ERNEST H. FALCONER, M D , F A C P ,
Governor for Northern California

DR HORTON RYAN CASPARIS

Horton Ryan Casparis, F A C P , of Nashville, Tennessee, died November 11, 1942, in Richmond, Virginia, where he was attending a Meeting of the Southern Medical Association.

He was born at Round Mountain, Texas, in 1891. He graduated from the University of Texas in 1915 and received his degree in Medicine at the Johns Hopkins University in 1919. He served his internship at the Willard Parker Hospital in New York City. Later, he became staff assistant at the Trudeau Sanatorium and then returned to Johns Hopkins for postgraduate work where he remained until 1924. The next year he spent his time visiting various European Clinics.

Dr Casparis joined the Faculty of the Vanderbilt University School of Medicine in 1925 and became Professor of Pediatrics there in 1928.

He was Chairman of the Section on Pediatrics of the American Medical Association and the Southern Medical Association, Pediatrician-in-Chief, Vanderbilt University Hospital since 1925, former President, Tennessee Tuberculosis Association; Diplomate, American Board of Pediatrics, formerly, Chairman of the Advisory Committee on Maternal and Child Health Services of the U S Children's Bureau, President of the Southern Trudeau Society, President of the American Board of Pediatrics, Member of the Editorial Board of the American Journal of Diseases of Children, author of numerous published articles on tuberculosis in children, allergy and the various aspects of the mental health problems in children, member of the Davidson County Medical Society, the Tennessee State Medical Association, the American Pediatric Society, the American Academy of Pediatrics, National Tuberculosis Association, and Fellow of the American College of Physicians since 1929

Dr Casparis made friends easily and was greatly admired by both the members of the Vanderbilt faculty and the student body

Nashville, the State of Tennessee and the entire Nation have lost an invaluable, skillful worker who gave most of his time in improving methods of treatment and general knowledge pertaining to the two subjects he seemed most interested in Tuberculosis and child mental health

WILLIAM CALVERT CHANEY, M D , F A C P ,
Governor for Tennessee

DR MAURICE L RIPPS

Dr Maurice L Ripps, F A C P , who had practiced Pediatrics in Elizabeth, N J , for the past fifteen years, died on October 28, 1942, at the Elizabeth General Hospital following a brain operation

Dr Ripps was highly esteemed by his Associates, and the Clinical Society and Staff of the Elizabeth General Hospital have raised several hundred dollars to place needed equipment in the Children's Ward of the hospital as a memorial He had been Assistant Attending in Pediatrics at this hospital for twelve years, having been very actively interested in that specialty from the time of his graduation in medicine

Dr Ripps was born in Bayonne, N J , December 11, 1899 He received his B S degree, 1922 and his M D degree, 1923 from the University of Michigan The ensuing four years he spent in preparing himself thoroughly in Pediatrics His first internship was for eighteen months at the Jersey City Hospital, and his second at the Willard Parker Hospital, New York Residencies followed at the Stamford General Hospital, the Children's Hospital in Detroit and the University Hospital at Ann Arbor, Mich

During an interim between two of these appointments, he served as Clinical Assistant at the New York Post-Graduate Medical School

In 1927 he took up the practice of Pediatrics in Elizabeth, N J , where he worked until his death During his first three years of practice, he served as Clinical Instructor at Bellevue Hospital Medical College, New York City He soon became too much occupied with his increasing responsibilities in Elizabeth to continue the work in New York He was made Assistant Attending in Pediatrics at the Elizabeth General Hospital in 1930, and the following year received a similar appointment at the St Elizabeth Hospital, both of which positions he occupied at the time of his death He was Pediatrician to St Walpurga's Orphanage, Roselle, N J , to the Sea-view Tubercular Hospital on Staten Island, and, since 1938, consulting Pediatrician to Alexian Brothers Hospital, Elizabeth, N J

Dr Ripps was a member of the St Elizabeth Clinical Society, the Elizabeth General Clinical Society, the Union County Medical Society, the Medical Society of New Jersey and the American Academy of Pediatrics He was a Diplomate of the American Board of Pediatrics, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1934.

Dr Ripps's untimely death at the age of forty-three leaves a large gap in the medical circles to which he belonged He is survived by his wife and a son

GEORGE H LATHROPE, M D , F A C P ,
Governor for New Jersey

DR HUBERT WORK

Dr Hubert Work, F A C P , former United States Postmaster General and Secretary of the Interior, died in Denver, December 14, 1942, at the age of eighty-two

Dr Work was born in 1860 on a farm in Indiana County, Pennsylvania He worked his way through the Indiana State (Pa) Normal School, matriculated in 1882 at the Medical Department of the University of Michigan, which he left after two years, and graduated in 1885 as a Doctor of Medicine from the University of Pennsylvania

In 1888, he came West, practiced medicine at Greeley and Fort Morgan, Colorado, and later settled at Pueblo, where he founded the Woodcroft Hospital for mental diseases

He was a Past-President of the Colorado State Medical Society and the American Psychiatric Association He was President of the American Medical Association in 1921 and a Fellow of the American College of Physicians since 1921

Always a staunch Republican, Hubert Work became one of the leaders of his party in Colorado, progressing from national committee-man for his

state to the United States Cabinet and Chairmanship of the National Republican Committee. These important responsibilities took him out of the active practice of his profession, but his faithful attendance at many medical meetings and his loyal devotion to his medical colleagues attested to his never-failing interest in the welfare of the medical profession. His friends, lay and professional, were innumerable. It can be said that he achieved great success in his profession, in business and in the political field.

JAMES J. WARING, M.D., F.A.C.P.

Governor for Colorado

ANNALS OF INTERNAL MEDICINE

VOLUME 18

MARCH, 1943

NUMBER 3

TYPE VIII PNEUMOCOCCUS: DEVELOPMENT OF SULFADIAZINE RESISTANCE, TRANSMISSION BY CROSS INFECTION, AND PERSISTENCE IN CARRIERS *

By ARTHUR W. FRISCH, M.D., ALVIN E. PRICE, M.D., F.A.C.P., and
GORDON B. MYERS, M.D., F.A.C.P., *Battle Creek, Michigan*

THE purpose of the present study is to report the development of "sulfadiazine-tolerance" by a type VIII pneumococcus and the transmission of this strain to another patient by cross infection. The evidence to be presented in support of drug-fastness was obtained from the clinical course, laboratory findings, sputum examination, and growth studies of the pneumococci in media containing sulfonamides.

For the technic and detailed results of sputum examination, the reader is referred to previous publications. Serum therapy produced clumping and increased phagocytosis of pneumococci in the sputum, which was usually followed by a gradual decline in the number.⁸ The characteristic response to chemotherapy, as seen in Wright stained smears of rusty sputum, was a sharp decrease in the number of organisms per field within 24 to 36 hours after treatment.^{5,6} Resistance to the drugs was suspected if the above effect did not occur or if the pneumococci returned to the sputum after an initial decrease, even though adequate blood sulfonamide concentrations were being maintained.^{5,6} The development of resistance was confirmed by in vitro studies of pure cultures carried out in the manner previously reported by one of the authors.⁷

RESULTS

The first patient (G. B.) was admitted to the hospital on September 6, 1941 with a right lower lobar pneumonia due to type VIII pneumococci.

* Received for publication October 12, 1942.

From the Departments of Bacteriology and Internal Medicine, Wayne University College of Medicine, and the Medical Service of Receiving Hospital, Detroit, Mich.

Supported by a grant from the Commonwealth Fund to the Michigan Department of Health Laboratories.

The clinical course, laboratory data, and sputum studies are presented graphically in figure 1. Before therapy was instituted, the sputum contained 85 pneumococci per oil immersion field,[†] the leukocyte count was only 3,400, but the blood culture was sterile. Within 36 hours after the institution of sulfadiazine therapy, there was a sharp decrease in the number of pneumococci in the sputum. After 50 hours of therapy, however, the pneumococci began to return to the sputum in increasing numbers despite high blood levels of sulfadiazine. This was interpreted as presumptive evidence that the organisms had become fast to the drug.^{5,6} Additional support for this concept was obtained clinically from the observations that the pneumonia had spread to involve the entire right lung and the blood cultures, which had previously been sterile, contained type VIII pneumococci. A total of 570,000 units of type specific horse serum was administered during the next 48 hours. Sulfathiazole was substituted for sulfadiazine in order to determine whether the pneumococci had retained sensitivity to this drug. The effect of serum was readily demonstrable by the agglutination and the increased phagocytosis of the pneumococci in the sputum. The rapid decrease in the number of pneumococci observed on September 13 was in part attributable to sulfathiazole since the organisms also showed the morphological changes characteristic of drug effect. The patient began to improve clinically and eventually made a complete recovery.

The second patient (M. G.) was first admitted on September 10, 1941 with a type III pneumonia involving the left lower lobe and made a prompt recovery following sulfathiazole therapy. During his stay in the hospital he occupied the bed adjacent to G. B. and additional close contact was possible since M. G. assisted the nurses and orderlies on the ward during his convalescence.[†] He was discharged on September 22 and returned a week later with a type VIII pneumonia involving the right lower lobe. The clinical course, laboratory data, and sputum studies are presented graphically in figure 2. Before sulfadiazine therapy was instituted the sputum contained only 2 pneumococci per oil immersion field[‡], an adequate leukocytosis was present, and the blood culture was sterile. Examination of the sputum 48 hours later revealed that no therapeutic effect from the drug had occurred. In fact, the number of pneumococci had increased to 32 per field and the pneumonia had spread to involve the right middle and left lower lobes. The contact between G. B. and M. G. was then recalled. In view of the probability of cross infection and the failure to obtain a drug response either clinically or in the sputum, the pneumococci were considered resistant to sulfadiazine. A total of 390,000 units of type specific horse serum was administered within the next 24 hours and sulfathiazole was again substituted for sulfadiazine. The clumping and increased phagocytosis of the pneumococci in the sputum together with the marked decrease in number on October 7

[†] According to previous studies ⁴ this indicates a serious pneumonia.

[‡] The pneumococci from G. B. were already sulfadiazine-fast (table 1).

[‡] According to previous studies ⁴ this indicates a good prognosis.

TABLE I
In Vitro Susceptibility of Type VIII Pneumococci (Case G B)

Date	Chemotherapy	Culture Number	Source	Sulfadiazine mg %				Sulfathiazole mg %				Sulfapyridine mg %				Control No Drug
				20	10	5	2.5	20	10	5	2.5	20	10	5	2.5	
9/6/41	None	1	Sputum	Cl	Cl	Cl	+++	Cl	Cl	Cl	+	Cl	Cl	+++	+++	+++
9/6/41	None	2	Sputum	Cl	Cl	++	+++	Cl	Cl	Cl	+	Cl	+	+++	+++	+++
9/10/41	Diazine	3	Blood	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
9/10/41	Diazine	4	Blood	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
9/10/41	Diazine	5	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
9/12/41	Thiazole	6	Blood	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
9/12/41	Thiazole	7	Blood	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
10/19/41	None	8	Sputum*	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
10/19/41	None	9	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
10/19/41	None	10	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
10/19/41	None	11	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	12	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	13	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	14	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	15	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	16	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	17	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	None	18	Sputum	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11/19/41	Type VIII Sensitive Control			Cl	Cl	Cl	+++	Cl	Cl	Cl	Cl	Cl	Cl	Cl	+++	+++

* Cultures 8 through 18 isolated by mouse passage of sputum

† Sodium salts of drugs used

Cl = Clear or no visible growth, +, ++, etc = increasing degrees of turbidity

was taken as evidence that both serum and drug had exerted the desired effect. The patient showed progressive improvement and subsequently recovered without complications.

Growth Inhibition Experiments In addition to the clinical and sputum studies already discussed, 18 cultures of type VIII pneumococci were obtained from patient G. B. at intervals and tested for their ability to grow in media containing varying concentrations of sulfadiazine, sulfathiazole, and sulfapyridine. The results are recorded in table 1. It may be noted that the growth of two strains isolated before the institution of therapy was inhibited by sulfadiazine in a concentration of 5 mg per cent and by sulfathiazole in a concentration of 2.5 mg per cent. Cultures 3 through 7 were obtained during the sixth and eighth days of illness when the clinical diagnosis of resistance was made. At this time a striking change in the sensitivity of the pneumococci to chemotherapeutic agents had occurred. The growth of these five strains was not inhibited by concentrations of serum to 20 mg per cent of sulfadiazine and sulfapyridine, whereas the growth of four of the same cultures was definitely inhibited by similar concentrations of sulfathiazole. Therefore, the foregoing data substantiate the evidence obtained from the sputum that the pneumococci had become resistant to sulfadiazine, but still retained partial sensitivity to sulfathiazole. The data also lend support to the concept that sulfathiazole, as well as serum, contributed to the ultimate recovery of the patient.

Type VIII pneumococci were also isolated from the sputum of patient M. G. at the time when resistance to sulfadiazine was suspected. The results are recorded in table 2. Seven of nine strains obtained during hospitalization grew maximally in media containing 20 mg per cent of sulfadiazine, whereas the other two strains were able to grow in 10 mg per cent of the drug. On the other hand, the growth of seven of these same cultures was inhibited by concentrations of 5 mg per cent or less of sulfathiazole. These data substantiate the evidence obtained from the sputum that sulfathiazole also played a part in the recovery of patient M. G. The fact that cultures from both patients were equally resistant to sulfadiazine and equally susceptible to sulfathiazole supports the concept that cross infection had occurred on the hospital ward.

A follow-up study of patients G. B. and M. G. revealed that both continued to carry mouse virulent, sulfadiazine-fast, type VIII pneumococci in their sputums for at least two months after the onset of their illness. All four strains isolated from G. B. one month after hospitalization (table 1) grew freely in 10 mg per cent of sulfadiazine and two multiplied fully in 20 mg per cent of the drug. One month later seven strains were obtained from G. B. and all multiplied in 10 mg per cent of sulfadiazine, but were partially inhibited by 20 mg per cent of the drug. Five cultures isolated from patient M. G. two months after hospitalization (table 2) grew freely in 10 mg per cent of sulfadiazine and one of these was able to grow maxi-

TABLE II
In Vitro Susceptibility of Type VIII Pneumococci (Case M G)

Date	Chemotherapy	Culture Number	Source	Sulfadiazine mg %					Sulfathiazole mg %					Sulfiapyridine mg %					Control No drug
				20	10	5	2.5		20	10	5	2.5		20	10	5	2.5		
10/4/41	Diazine	1	Sputum	++	++	++	++	+	Cl	+	+	++	+	+	++	++	++	+	++
10/5/41	Thiazole	2	Sputum	++	++	++	++	+	Cl	+	+	++	+	+	++	++	++	+	++
10/5/41	Thiazole	3	Sputum	++	++	++	++	+	Cl	+	+	++	+	+	++	++	++	+	++
10/5/41	Thiazole	4	Sputum	++	++	++	++	+	Cl	+	+	++	+	+	++	++	++	+	++
10/5/41	Thiazole	5	Sputum	++	++	++	++	+	Cl	+	+	++	+	+	++	++	++	+	++
10/19/41	None	6	Sputum*	Cl	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
10/19/41	None	7	Sputum	+	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
10/19/41	None	8	Sputum	++	++	++	++	+	+	+	+	+	+	+	++	++	++	+	++
10/19/41	None	9	Sputum	++	++	++	++	+	+	+	+	+	+	+	++	++	++	+	++
12/3/41	None	10	Sputum	+	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
12/3/41	None	11	Sputum	++	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
12/3/41	None	12	Sputum	++	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
12/3/41	None	13	Sputum	++	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
12/3/41	None	14	Sputum	++	++	++	++	+	Cl	Cl	Cl	+	+	Cl	+	+	+	+	++
12/3/41	Type VIII Sensitive Control			Cl	Cl	++	++	+	Cl	Cl	Cl	Cl	+	Cl	Cl	Cl	Cl	+	++

* Cultures 6 through 14 were isolated by mouse passage of sputum

† Sodium salts of drugs used

Cl = clear or no visible growth, +, ++, etc = increasing degrees of turbidity

mally in 20 mg per cent of the drug. It may also be noted that after two months (tables 1 and 2) the pneumococci were slightly more susceptible to sulfapyridine than to sulfadiazine, but that the growth of most cultures was best inhibited by sulfathiazole.

DISCUSSION

The two cases presented in this communication are additional examples of the correlation previously reported⁶ between the development of resistance as seen in the sputum and the ability of the pneumococci to grow in media containing increasing concentrations of the sulfonamide drugs.

The in vivo development of varying degrees of drug fastness has been reported by numerous investigators^{1, 5, 6, 7, 9, 10, 11, 12}. Furthermore, the therapeutic efficiency of a particular sulfonamide appears to be closely related to its capacity to induce resistance. Thus, one of us found that in 17 per cent of cases given sulfanilamide the pneumococci returned to the sputum following an initial bacteriostatic effect despite adequate blood levels of the drug. A similar phenomenon was observed in 6 per cent of the cases treated with sulfapyridine and in only 2 per cent of those who received sulfathiazole^{5, 6}. It was subsequently shown that these strains had acquired a considerable degree of tolerance to the sulfonamide drugs.⁷ Direct confirmation of this observation was recently reported by Sesler and Schmidt, who demonstrated by in vitro experiments that "sulfanilamide resistance was developed most rapidly, sulfapyridine next in order, and sulfathiazole most slowly."¹³ Carpenter and his co-workers have found that strains of gonococci "acquired only slight, if any, tolerance for sulfathiazole, although resistance to sulfanilamide was readily established."² Further study of sputum from patients with pneumonia has revealed that sulfadiazine occupies a position intermediate between sulfapyridine and sulfathiazole in that resistance develops in approximately 3 to 4 per cent of the cases. Although it is generally conceded that when organisms become fast to one sulfonamide they also acquire a comparable degree of tolerance to others, the results of the present study indicate that specific resistance to a particular drug may be induced. Similar observations have been made with *E. coli*¹⁴ and with gonococci.² We believe, therefore, that the substitution of one drug for another may be of occasional value since both of our patients responded to sulfathiazole despite the fact that the pneumococci had become partially tolerant to sulfadiazine.

The prolonged retention of sulfonamide resistance by pneumococci has been emphasized by the studies of Schmidt, Sesler and Dettwiler, who found that completely resistant organisms maintained this property after more than 200 passages through normal mice.¹² Unpublished data of Hamburger, Sesler, Schmidt and Ruegsegger have revealed that sulfonamide-resistant pneumococci could be isolated from nose and throat cultures of carriers four months after recovery from the pneumonia.¹² Similarly the patients

G B and M B carried virulent, sulfadiazine-fast pneumococci in their sputums for at least two months after their discharge from the hospital. During that period they were potential sources of future cases of type VIII pneumonia which might have proved to be refractory to chemotherapy. If the frequency of drug-fast strains increases significantly in the general population by the indiscriminate use of sulfonamides, then it seems likely that the value of chemotherapy in pneumococcic pneumonia may be considerably reduced. During the past five years we have not noted any such tendency as judged by the examination of repeated specimens of rusty sputum from patients with pneumococcic pneumonia. Further investigation will be necessary in order to establish the duration of the carrier state and to devise methods of eradicating drug-tolerant pneumococci from the upper respiratory tract.

SUMMARY

A case of pneumonia was reported due to a type VIII pneumococcus which was originally sensitive to sulfadiazine, but became resistant during the course of treatment. This same strain was then transmitted by contact to a second patient in an adjacent bed and later produced a pneumonia which also failed to respond to treatment with sulfadiazine. Drug-fastness was evidenced by the development of a positive blood culture during therapy in one patient, an extension of the pneumonia to other lobes in both patients, a marked increase in the number of pneumococci in the sputum in both patients, and the growth of these organisms in media containing 10 to 20 mg per cent of sulfadiazine. On the other hand, the growth of these same cultures was inhibited by 5 to 10 mg per cent of sulfathiazole.

After sulfadiazine-resistance had become apparent, serum and sulfathiazole were administered to both patients and recovery followed. Evidence was obtained from the sputum that each of the latter agents exerted its characteristic therapeutic effect. In addition, a follow-up study revealed that both patients continued to carry virulent sulfadiazine-resistant strains of type VIII pneumococci in their sputums for at least two months after hospitalization.

BIBLIOGRAPHY

- 1 AUGER, W J Sulfapyridine resistance of pneumococci following sulfapyridine therapy in infants and children and the comparative potency of three chemotherapeutic agents for pneumococci as shown by laboratory tests, *Jr Pediat*, 1941, xviii, 162
- 2 CARPENTER, C M, CHARLES, R., and ALLISON, S D Effect of gradually increased concentrations of sulfathiazole on the gonococcus in vitro, *Proc Soc Exper Biol and Med*, 1942, xlviii, 476
- 3 FRISCH, A W Sputum studies in pneumonia phagocytosis and the effect of serum therapy, *Proc. Soc. Exper Biol and Med*, 1938, xxxix, 473
- 4 FRISCH, A W Sputum studies in pneumonia as an aid in prognosis, *Am Jr Clin Path*, 1940, x, 472
- 5 FRISCH, A W Sputum studies in pneumonia The effect of sulfanilamide, *Jr Lab and Clin Med*, 1940, xxv, 361

- 6 FRISCH, A W . Sputum studies in pneumonia The effect of sulfapyridine and sulfathiazole, *Am Jr Clin Path*, 1942, xii, 16
- 7 FRISCH, A W Sputum studies in pneumonia. In vivo and in vitro susceptibility of pneumococci to sulfapyridine and sulfathiazole, *Am Jr Clin Path*, 1941, xi, 797
- 8 HAMBURGER, M, JR, SCHMIDT, L H, RUEGSEGGER, J M, SESLER, C L, and GRAFFA, E S Sulfonamide resistance developing during treatment of pneumococcic endocarditis, *Jr Am Med Assoc*, 1942, cxix, 409
- 9 LOWELL, F C, STRAUSS, E, and FINLAND, M Observations on the susceptibility of pneumococci to sulfapyridine, sulfathiazole and sulfamethylthiazole, *ANN INT MED*, 1940, xiv, 1001
- 10 ROSS, R W Acquired tolerance of pneumococcus to M & B 693, *Lancet*, 1939, i, 1207
- 11 SCHMIDT, L H, HILLES, C, and DETTWILER, H A The response of different types and strains of pneumococci to sulfapyridine, *Jr Infect Dis*, 1940, lxi, 232
- 12 SCHMIDT, L H, SESLER, C, and DETTWILER, H A Studies on sulfonamide-resistant organisms I Development of sulfapyridine resistance by pneumococci, *Jr Pharmacol and Exper Therap*, 1942, lxxiv, 175
- 13 SESLER, C L, and SCHMIDT, L H Studies on sulfonamide resistant organisms II Comparative development of resistance to different sulfonamides by pneumococci, *Jr Pharmacol and Exper Therap*, 1942, lxxv, 356
- 14 STRAUSS, E, DINGLE, J H, and FINLAND, M Studies on the mechanism of sulfonamide bacteriostasis, inhibition and resistance experiments with *E coli* on a synthetic medium, *Jr Immunol*, 1941, xli, 313

A REVIEW OF THE DRASTIC SHOCK THERAPIES IN THE TREATMENT OF THE PSYCHOSES *

By FRANKLIN G EBAUGH, M D, F A C P,
Denver, Colorado

DURING the past decade we have seen progressive changes in medical education and practice which have led to closer relationships between psychiatry and general medicine. We now accept psychiatry as that part of medicine which deals with the pathology and therapy of the person, instead of thinking of it as an isolated specialty dealing with advanced psychopathological disorders usually already admitted to institutions for treatment in the later stages of development when therapy is most difficult, more prolonged and less effective. Through this breakdown of the isolation of psychiatric medicine from basic general medicine we are now beginning to see the closest collaboration between the psychiatrist and internist in the study and understanding of the universal personal aspects of all medicine (shown in personality functions) and of the impersonal aspects shown in pathological expressions of disordered function of parts of the body (diseases of organs and systems). The effectiveness of present day clinical medicine, therefore, means an integration of these essential personal and impersonal components for examination and therapy of all types of illness.

In this lecture on the drastic shock therapies it is my obligation to present a résumé of their present results and status ¹

The mode of action of these therapies is unknown, the clinical reactions are dramatic, the complications and contraindications are of great medical interest and import and should lead to a greater mutual dependence and collaboration between the psychiatrist and internist. The pharmacological shock therapies of insulin and metrazol as well as convulsive electro-shock therapy present numerous physiological, biochemical, psychological, electroencephalographic, electrocardiographic and neuropathological problems for research.

The use of these drastic therapies has been summarized recently by the United States Public Health Service in a survey of October, 1941. Questionnaires were sent to 356 hospitals and 85.7 per cent or 305 responded, of which 260 hospitals or 85.2 per cent were using shock therapies. An estimated total of 26,335 patients were receiving insulin shock therapy during the period of October, 1935 to October, 1941, 36,127 were receiving metrazol therapy and 7,771 patients were receiving electric shock therapy. The trend in the use of shock therapy in mental hospitals is summarized in table 1. The type of shock preferred is summarized in table 2 ²

* Morning lecture before the American College of Physicians meeting, St. Paul, Minnesota, April 24, 1942.

From the University of Colorado School of Medicine and Colorado Psychopathic Hospital.

TABLE I
Trend in the Use of Shock Therapy in Mental Hospitals

Therapy Used	Hospitals Reporting Use of Specified Shock Therapy	Use of Shock Therapy Reported					Shock Therapy Being Replaced By				
		In-creasing	Same	De-creasing	Dis-continued	Not Stated	Insulin	Me- trazol	Elec- tric	Me- trazol and Elec- tric	Other
Insulin Per cent	219 100	23 10 5	59 26 9	50 22 8	75 34 2	12 5 5	—	23	27	18	4*
Metrazol Per cent	228 100	32 14 0	47 20 6	67 29 4	74 32 5	8 3 5	4	—	88	—	1†
Electric Per cent	129 100	84 65 1	24 18 6	5 3 9	1 0 8	15 11 6	—	2	—	—	1‡

* Insulin-Metrazol (2), Metrazol and Curare, Typhoid

† Insulin-Metrazol

‡ Metrazol, Petrotxin, Camphor

TABLE II
Type of Shock Therapy Preferred *†

Preferences Expressed by Hospitals Using	Number of Hospitals Reporting	Shock Therapy Preferred								Undecided and Not Stated	
		Insulin		Metrazol		Electric		Combinations			
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Insulin, Metrazol and Electric	111	14	2 6	9	8 1	66	59 5	8	7 2	14	12 6
Insulin and Metrazol	78	26	33 3	20	25 6	6	7 7	6	7 7	20	25 6
Metrazol only	30	—	—	11	36 7	6	20 0	3	10 0	10	33 3
Insulin only	21	8	38 1	—	—	2	9 5	—	—	11	52 4
Metrazol and Electric	9	—	—	1	†	6	†	—	—	2	†
Electric only	3	—	—	—	—	2	†	—	—	1	†
Miscellaneous	8	5	†	—	—	2	†	1	†	1	—
None	46	2	4 3	—	—	4	8 7	—	—	40	87 0
Total	306	55	18 0	41	13 4	94	30 7	18	5 9	98	32 0

* Replies to question "If only one form of shock therapy were available, which would you use?"

† Less than 10 cases in denominator

‡ Reprinted by permission from the Am Jr Psychiat , 1942, xcix, 95

In this lecture I should like to center my discussion around the three prevalent modes of shock therapy for the psychoses, i e , insulin, metrazol, and electric shock convulsive therapy, with a brief résumé of the technics of administration, the indications and contraindications, reactions of the patients, complications of therapy and mechanisms of improvement As is often true in the introduction of newer types of therapy, there is now evidence that the extreme enthusiasm of the early days has given way to careful appraisal of the assets and dangers of these types of therapy. These shock therapies have reaffirmed the psychosomatic view point of psychiatry and aroused a tremendous interest in research and speculation of all those who treat the mentally ill

INSULIN SHOCK THERAPY

Insulin shock therapy was accidentally discovered by Manfred Sakel in 1933 Sakel attempted to use small doses of insulin in 1928 in an attempt

to relieve withdrawal symptoms of morphine addicts. When he produced deeper hypoglycemic reactions than planned he noticed marked alterations and improvement in the mental condition of his patients. Insulin shock therapy aroused tremendous interest on the continent and was first introduced in the United States by workers at Worcester State Hospital in 1936. At the American Psychiatric Association's 1937 meeting in Pittsburgh there was a symposium on hypoglycemia therapy and it was agreed at this time that the technic of treatment had been fairly well utilized and stabilized throughout the country. It was accepted that insulin therapy should be given only to psychotic patients of the schizophrenic reaction type. Preparation of the patient was reported as of the utmost importance and centered around an extremely thorough and meticulous physical examination including routine electrocardiographic studies, since it is well known that insulin may cause, even in small doses, disturbances of rhythm in cardiac deficiency. Likewise routine chest roentgenograms, complete blood chemistry, routine blood counts and urinalysis were carefully made in every case, but routine glucose tolerance tests were not given unless indicated by the blood chemistry and urinalysis studies. This special type of treatment was explained to the patient and his attitude and acceptance carefully evaluated. Contraindicative to insulin shock were essential hypertension, angina pectoris, coronary sclerosis or occlusion, valvular heart disease and myocarditis, hyperthyroidism, tuberculosis, and impaired renal, liver or pancreatic functions.

Technic of Treatment It is the uniform organization in mental hospitals at the present time to have a special unit for insulin shock therapy consisting of a trained nursing staff and assistants. One nurse for each two to three patients is essential. It is likewise essential that a physician, familiar with this technic, must be present or immediately available at all times. Following the selection of the patient from both the physical and mental points of view regular insulin, and never protamine zinc insulin, is given to the fasting patient early each morning six times a week. The average total course of treatment is from two to three months. The initial dose is 15 units, which is increased daily by 5 to 10 units until signs of hypoglycemic coma begin to appear. The treatment is terminated for the average patient by urging him to drink a sugar solution three to four hours after the injection. The amount of sugar in grams used for termination is double the number of units of insulin administered. The solution should be warm to hasten absorption, and the glucose may be administered in water, weak tea or any fruit juice, but milk is not advisable. During phase one in insulin shock therapy the patient is usually able to drink, but if he should refuse to do so the solution must be given with a nasal tube or by the intravenous route. Thirty minutes later the patient is served breakfast and urged to eat. This constitutes phase one in the administration of insulin shock therapy.

Phase two is reached when the patient loses consciousness in the third hour. When this occurs the insulin dosage is kept stationary and termina-

tion is by means of the nasal tube or intravenous route The experience of the physician and also close observation of the patient indicate that proper development of coma is characterized by loss of consciousness in the third hour and deep coma in the fourth or fifth hour The shock dose varies tremendously in individual patients Deep coma may be developed by as little as 20 units, whereas in other patients as many as 600 units fail to produce hypoglycemic symptoms In our experience we rarely overstep 200 units since many untoward reactions are seen with a higher dosage, and experience shows that doses above 200 units rarely produce satisfactory and typical coma Methods can be worked out in individual patients to sensitize them by zigzagging the dosage from day to day, cutting down on the caloric intake or the use of small doses of insulin the night before treatment Our

TABLE III
Symptoms

Hours	Symptoms	Localization
First	<div>Latent time</div> <div>Somnolence (97.2%) Hypotonia (97.4%)</div> <div>Perspiration (99.1%) Salivation (90.1%)</div>	Suppression of cortical and cerebellar activity
Second	<div>Clouded consciousness Fine tremor Aphasia Apraxia Agnosia</div> <div>Perceptual disturbances Motor excitement Confusion Psychotic syndromes</div> <div>Fall of temperature Diminished exteroceptive sensitivity</div>	
Third	<div>Loss of consciousness (100%) Primitive movements (71.5%) Forced graspings (71%) Clonic twitchings (79.2%) Myoclonoid twitchings Choreiform Athetoid Hemiballistic } movements (35.6%) Early torsion spasms</div> <div>Motor restlessness Exophthalmos Dilated pupils Light reaction present Pulse rate increased Exteroceptive sensitivity increased</div>	Release of the basal ganglia and hypothalamus
Fourth	<div>Deepening stupor Increased tonus Coarse tremor Tonic spasms (82.6%) Tetanic postures Conjugate deviation of the eyes Late torsion spasms</div> <div>Pupils small or large Pulse rate increasing or decreasing Signs of paralysis of the pyramidal functions Decreased exteroceptive sensitivity Increased interoceptive sensitivity</div>	Release of the midbrain Suppression of pyramidal functions
Fifth	<div>Tonic extensor spasms (34.1%) Posture reflexes Depression of tendon reflexes Deep coma Diminished sensitivity</div> <div>Lid and corneal reflexes sluggish Shallow respiration No corneal reflexes</div> <div>Pin-point pupils No light reaction Pulse rate decreased</div>	Release of the medulla oblongata

experience was similar to that of other observers in that we find direct correlation between the patient's acceptance of treatment and the dosage needed to produce coma. Frostig⁸ has given us a table of symptoms correlated with each hour in accordance following table 3. These are of help and value in the selection of time of termination.

Time and Technic of Termination There should be no definite rule for the time of awakening such as 10:30 or 11 a.m. Each patient has to be carefully followed through his coma and awakened at the most opportune time. It is a safe rule never to leave the patient in a deep coma more than 45 minutes, nor should any patient be allowed to continue more than 30 minutes with absent corneal reflexes. Careful charts should be kept with a notation in red when the patient becomes comatose as well as a regular testing of the corneal reflexes. Sakel emphasized the termination of treatment in relation to the patient's mental reaction type. For instance, the patient in a catatonic stupor is brought out of the hypoglycemia at the point where he shows the most mental activity, paranoid patients with systemized delusions are allowed to go into deep coma and in patients with catatonic excitement hypoglycemia is terminated when they grow somnolent.

You cannot estimate the depth of coma by reflex changes of the upper neuron type. A positive Babinski sign may appear in a very light coma in some patients and not appear in others until a very deep coma and a medullary phase have developed. In deep coma there may be a hypotonia and areflexia, or the patient may be tense, excited with myoclonic movements that make testing of the reflexes impractical. The stage of insulin coma can be carefully evaluated by eye movements as follows:⁴

- 1 Nystagmus on attempted fixation. Here also may be seen such things as lid retraction, myoclonic, conjugate deviation, a positive Babinski sign, etc. Patient is usually able to talk a bit and perhaps swallow.
- 2 Spontaneous pendular nystagmus or conjugate deviation which do not disappear upon stimulation. Here corneal reflexes remain active. Patient is unable to fix.
- 3 Nystagmus upon stimulation only. Here spontaneous eye movements have ceased and eyes remain at rest near midposition. If the head is rolled quickly a short period of pendular nystagmus will follow.
- 4 No nystagmus on stimulation. Here is a contracted fixed pupil, and decreased or absent corneal reflexes. Tendon jerks may be normal or decreased.
- 5 Paralytic respiratory coma. An intercostal paralysis with respiratory depression. Patient shows gasping with shallow, irregular respiration and dilating pupils.

We have here phenomena similar to that occurring in anesthesia. It is important that the physician remain with the patient during phase two. It

is obvious that no patient should be allowed to reach stage five. The above stages correspond closely to the accepted phases such as mild hypoglycemia, the precomatose state, the onset of coma, the deep coma, and the stage of tetanoid seizure or respiratory paralysis. The usual termination of coma is by means of the nasal tube route. The technic here must be a careful one in ascertaining the position of the tube before the sugar solution is administered. This is best done by aspirating some of the gastric contents by means of the suction bulb and testing it on litmus paper. If no fluid can be aspirated, by introducing air through a syringe one can listen with the stethoscope over the stomach. The intravenous injection of glucose should be used for termination in all emergency situations. Some clinics use the intravenous termination routinely but since this tends to thrombose veins and since the sudden awakening produced by injection has less favorable effect than the gradual one resulting from gavage we favor this route of administration. The patient must always be given carbohydrate by mouth after awakening and must always be given a substantial meal. In case the patient routinely arouses slowly, additional intravenous injections should be given. Usually the patient on awakening has a short period when he is free from his troublesome preoccupations. It is our policy to employ psychotherapy at this time.

The complications of insulin therapy are usually reviewed under four main headings. The first centers around the central nervous system disorders such as aphasia and hemiparesis, which are usually transitory, although they may persist for two to three days. It is our policy to terminate insulin shock when such complications occur. Epileptiform seizures often occur during the first two hours of treatment. If the patient remains in good condition following the convulsion the treatment need not be terminated. It has been noted and emphasized by many that following epileptiform seizures clinical improvement follows. Status epilepticus is rare. The late tetanoid convulsions occurring after the third hour represent acute danger signals indicating the abrupt termination by the intravenous route. Cardiovascular disturbances represent an important complication. An irregular pulse is common and of little significance during the first hour of treatment, whereas a rapid, thready pulse in late hours of treatment indicates cardiac fatigue. Auricular fibrillation may occur. Cardiac failure is rare but does occur, as does general circulatory collapse. Immediate termination by the intravenous route is indicated in the above complications. Among respiratory disturbances the most common complication is aspiration, since many patients have a marked overproduction of saliva associated with the loss of the swallowing and cough reflex. The head of the bed should be raised so that the patient is sitting upright and his head allowed to hang, thereby letting him drool. Sheet restraints are employed to help the patient maintain this position. Laryngospasm may develop as part of the general tonic muscle spasm and this, of course, calls for immediate termination. Central respiratory failure may set in without warning and

necessitates prompt termination by intravenous glucose. Injections of lobeline and the use of oxygen are the treatment of choice here. Pulmonary edema likewise has been reported. Intravenous glucose slowly injected will usually care for this condition. The use of adrenalin is contraindicated. The fourth and miscellaneous set of complications center around the allergic reactions manifested by local irritation at the site of injection of insulin. So-called insulin lipomata may develop with resulting atrophy of the subcutaneous tissues and muscles. Adrenalin and intravenous calcium are used in the treatment of this complication. The most serious and, fortunately, infrequent complication is delayed awakening or prolonged coma. If the patient does not awaken after tube feeding or becomes unconscious after swallowing, intravenous glucose should be given not later than 30 minutes after the original sugar intake. If the patient does not arouse, an immediate blood sugar determination should be made to show the presence or absence of hypoglycemia. At times the patient may show a high blood sugar and yet remain comatose, cyanotic, dyspneic and may be having convulsions. If the blood sugar level is normal or above normal, it is obvious that no additional sugar should be given. The patient should be kept quiet and warm and stimulants withheld unless actually needed to preserve life. Oxygen inhalations are sometimes of benefit. Intravenous injections of Betalin have been advocated. Convulsions are usually controlled by two grams of potassium chloride. Blood transfusions have been used with some success. Death during insulin shock therapy is usually due to this complication and our experience indicates the most important precautions to avoid excessive doses of insulin, terminate the treatment at the proper time, and avoid prolonged periods of deep coma, never allowing a duration of more than 45 minutes and less in many cases.

Changes During Treatments Numerous papers have been written concerning the physiological changes during treatment including the well known increase in weight, changes in brain metabolism, decrease in blood sugar levels to about 25 mg per cent during hypoglycemia, and the development of mild leukocytosis without changes in the red blood cell count and hemoglobin during hypoglycemia. The serum lipoids, other than cholesterol, are raised during treatment, and this fact is of great interest since it has long been known that in schizophrenic reactions the serum lipoids are low and in cases that recover the rise is especially noticeable.

At the present time there is no clear cut evidence of actual brain damage, although animal experiments tend to show that prolonged coma produces irreversible histopathological changes. In all clinics it is accepted that the depth of coma determines in all cases whether the pathological changes are reversible or whether definite nerve cell destruction may occur.

Mental Changes and Possible Mechanisms of Improvement Fairly characteristic changes are noted in patients who improve under insulin therapy. During the precomatose stage the patients show interesting emotional changes which may vary from cooperation and contentment to an-

tagonism and rage with all stages of gradation between the states of calmness and excitement. The patient's prevalent mood disturbance swings to the opposite extreme. The previously tense patient may become placid, and the hyperkinetic, restless patient will become quiet. Often during the precomatose stage the patient discusses his conflict material and troublesome preoccupations. Patients who have been questioned regarding their experiences during the coma will usually be nonproductive and many of them state they are experiencing death. It is to be emphasized here that patients who accept the treatment will be less disturbed during both precomatose and comatose phases. When the treatment has been terminated many patients are frequently cooperative and show a marked change in attitude from withdrawal, suspicion and absorption in their conflict material to acceptance of treatment and interest. This may last for a few minutes or for more prolonged periods especially in the patients who later show improvement. Adjustment to the group including both relationships to other patients and to the professional and non-professional personnel of the hospital are important. The factor of the mechanism of improvement, in my opinion, is not on the basis of biochemical changes as much as it is a psychotherapeutic one. The interest of the entire staff, and the prolonged individual attention in the care the patient receives from the medical staff and nurses during and between the shocks are of paramount importance. These psychotherapeutic adjuncts are clearcut and less theoretical than the stress placed in the literature on anoxemia. The reduced consumption of glucose and oxygen by the brain is not the only metabolic disorder that takes place during insulin hypoglycemic shock. Katzenelbogen⁵ postulates that the mode of action is that usually attributed to non-specific protein therapy namely, activation of the functions of organs (protoplasma activation), or the changes which take place in the constitution of the body fluids, or both. This may well be applied also to non-specific shock therapy.

Results of Treatment The literature shows a marked discrepancy in the results of treatment, varying from 70 per cent complete recovery to 20 per cent improvement, with even poorer results in untreated cases. There is no doubt that this is due to lack of uniformity in the application of insulin shock as well as in the diagnosis of schizophrenic reactions. Likewise, the literature of spontaneous remissions varies from 10 to 40 per cent according to the center from which one obtains results. The results reported by Ross and Malzberg⁶ from New York State are about the average from the world over. There were 1757 patients treated with insulin and the results were recovered, 11.1 per cent, much improved, 26.5 per cent, improved, 26 per cent, unimproved, 26.2 per cent, died, 1.1 per cent. The number of recovered cases, as well as the total number showing improvement, was about three times that in a control group receiving the usual institutional treatment. Reports of a one and two year follow-up⁷ indicate that the percentage of patients described as recovered remained almost constant, but that there has been a reduction in the percentage of cases showing a lesser

degree of improvement The total percentage of recoveries and improvements had fallen from 63.5 per cent to 48.2 per cent, one year later The latter percentage, however, was still most favorable when compared with the results from other types of therapy Cases in which psychotic manifestations were of short duration had the best possibilities of recovery

Prognostic factors have been carefully evaluated by Cheney and Clow⁸ who state that the following are the most important ones since they appear to be indicative of favorable results

- 1 Acute onset in contrast to gradual change in personality or attitude
- 2 Onset with a precipitating factor (such as an obvious conflict or loss of love object)
- 3 The productivity in psychotic symptoms and flexibility, especially in paranoid ideas, in contrast to a rigid paranoid system
- 4 Preserved affectivity
- 5 A prepsychotic personality with capacities for interpersonal relationships and sublimation
- 6 Marked depressive and neurotic features

Preservation of normal emotional reactions previously emphasized appears to be one of the most important things along with an acute onset Previous attacks with remission apparently do not have any effect on the general outcome with insulin shock treatment In our clinic⁹ and others¹⁰ attempts have been made to use special psychological tests, especially the Rorschach test, to obtain prognostic hints regarding the response to this type of therapy The greatest care must be taken to limit patients receiving insulin shock therapy to clearcut psychosis of schizophrenic type, since it is generally accepted that other psychotic reaction types either do not respond to insulin or respond better to the other methods of treatment

METRAZOL AND ELECTRIC CONVULSIVE SHOCK THERAPY

The development of convulsive therapy in general paralleled that of insulin shock therapy Ladislau von Meduna, in 1933, began using camphor intravenously to produce convulsions and reported encouraging results Later he developed the use of metrazol, a synthetic product, soluble in water and rapidly absorbed, which could be given intravenously in 10 per cent solution and which within five to 15 seconds produced a convulsion The same careful method of preparation for this treatment as that described for insulin is carried out, including roentgenograms of the spine to rule out old injuries or structural deformities The patient is best left without sedation for 12 hours prior to injection and the treatment is given on a fasting stomach All false dentures should be removed and the practice should be to hyperextend the patient's dorsal spine, since in this position the risk of vertebral fracture is reduced The initial dose, from 3 to 5 cc of the drug, is given intravenously and rapidly If no convulsion takes place in one

minute the injection is repeated with one half to one c c more than the amount originally given. Experiments indicate that the fatal dose is about 30 c c, but in our experience we have never given more than 12 c c in one injection. The convulsion is severe and usually starts with a wide opening of the mouth at which time a flexible gag is inserted. There is usually a cough or cry, a gradual increase in general tonus, and then there appear clonic movements which rapidly increase in intensity. These clonic movements are then followed by a tonic phase which may be prolonged, producing



FIG 1 A Following injection of Metrazol and prior to convulsion B Beginning of seizure C End of seizure D Post-convulsive excitement

extreme rigidity. A second clonic phase, which gradually decreases in intensity, ends the seizure. This sequence, although like an epileptic fit, differs from it in that the epileptic convulsion does not have the initial clonic phase. At the beginning of the seizure the pupils dilate and become fixed. During the convulsion urination and ejaculation frequently occur. Pyramidal tract signs such as ankle clonus and unilateral or bilateral Babinski signs appear. The paroxysm ends with a period of apnea which lasts several seconds, during which the patient becomes cyanotic and livid and the eye-

balls turn upwards. A deep inspiration terminates this period of apnea which is followed by snoring-like respirations. Following the convulsion the patient is frequently excited, shows marked anxiety and confusion, and on occasions nausea with vomiting may develop. Care should be exercised to prevent aspiration.

Frequency of Treatment It was our usual policy to give metrazol treatments twice a week and it has been our routine to limit such treatments to a total of 8, although in many clinics as many as 25 convulsions are in-



FIG 2 A Before treatment showing apprehension, confusion and bewilderment
B Beginning of coma C Deep wet shock D Positive Gordon

duced. We usually find that patients who improve, especially the affective depressive reactions, begin to improve following the third or fourth seizure.

Indications and Contraindications Although metrazol convulsive therapy was originally proposed by Meduna for schizophrenic reaction types the experience of most clinics indicates the main field of effectiveness is in the affective disorders. It has not, however, been entirely abandoned in schizophrenia. In the study of our 400 cases improvement occurred in schizophrenia and it is still utilized in the catatonic reactions.

The results in the depressive psychoses are frequently striking. Metrazol should not be used indiscriminately in these reactions, but in the deep-seated, prolonged depressive states and in those patients who become exhausted from agitation and who make repeated suicidal attempts it is clearly indicated. This group includes the agitated depression, and various types of involutional depressive disorders. The results in the manic reactions are not as outstanding as in the depressive group. We doubt very much the advisability of the use of metrazol therapy in severe psychoneurotic reactions. The contraindications are practically the same as for insulin therapy, namely, the presence of cardiovascular disease, abnormalities of the blood or urinary constituents, febrile conditions, thrombophlebitis, tuberculosis, cachexia, bone diseases, and the presence or history of a skull or back fracture. The most serious complications consist of dislocations and fractures which result from the extreme violence of muscular contractions during the seizure. Dislocation of the jaw may occur, although reduction is simple and easily carried out after the seizure while the patient is still unconscious. Dislocation of the shoulder is less frequent and can be prevented by keeping the arms in adduction close to the trunk, the forearms crossed on the chest. Rarely there are fractures of the humerus and even of the femur, but the most important and unfortunately the most frequent appear to be the fractures of the thoracic vertebrae. The original paper pointing out these fractures by Polatin, Freidman, Harris and Horwitz, of the New York State Psychiatric Institute, reported fractures occurring in as high as 49 per cent of the patients. In our series careful roentgenological studies were made of all cases, showing the incidence of fractures to be less than 7 per cent. Fractures usually occur in the mid-thoracic area and are of a compressed type. The absence of subjective complaints from these patients, even with one or more vertebral bodies compressed, is striking, and there appears to be no relationship between the intensity of the complaint of backache and the degree of bone injury. If such fractures occur the orthopedic consultant puts the patient in a cast or corset brace for several weeks, during which time the patient is ambulatory. The sequela is usually a slight gibbus. Naturally there has been considerable work done to prevent fractures. The most striking, as well as the most important advance in the prevention of fractures, has been the introduction of curare by Bennett¹¹. This drug is now in widespread use in most psychiatric clinics. It is given intravenously, relaxing the peripheral muscles through its selective, depressive action on motor nerve endings. One c c of the aqueous solution of curare represents 10 mg of the crude drug. The dosage is usually 1 c c per 20 pounds of body weight, and it is administered intravenously over a period of one to one and one-half minutes. Following the intravenous injection of curare, metrazol is given in two to three minutes. Typical clonic-tonic-clonic sequence is present, but the degree of rigidity is markedly reduced and the

violent clonic spasm is absent or greatly reduced. The extremities of the patient who has been curarized can be passively moved at will during the convulsion. It is wise to give prostigmine following the use of curare and we find that many patients vary in their sensitivity to this drug. The other complications frequently observed represent memory impairment similar to that seen in the organic reaction types. The patients, as a rule, both before and following individual treatments, are extremely apprehensive and frequently speak of dying, and many show an accentuation of the pathoplastic features of their illness. Dr Neuburger and I¹² have summarized the results of animal experimentation which on the whole indicate that brain changes are present but are for the most part reversible. Apparently some degree of cortical damage does occur as shown in the cellular changes. These changes appear to be secondary to vascular changes.

Results of treatment can be tersely stated. The general agreement is that the use of metrazol convulsive therapy in the affective reaction is almost uniformly favorable and that rapid improvement occurs in a large majority of these cases. The results in the schizophrenic reactions do not substantiate the early claims of the proponents of this type of therapy and insulin shock treatment continues to be the method of choice in schizophrenic reactions.

ELECTRIC CONVULSIVE THERAPY

Since 1937 electric convulsive therapy has gained considerable prominence in the treatment of psychotic reactions. Although it has been known for many years that electricity produced convulsions, it was not until Cerletti and Bini¹³ inaugurated this type of therapy in Italy that it gained prominence. It was soon adopted throughout the continent and was introduced in this country at the New York State Psychiatric Institute early in 1939. There are two methods in use at the present time, one of which employs an alternating current and produced unconsciousness in the patient, and the other, developed by Berkwitz, uses faradic shock which is not associated with loss of consciousness. This latter method, although most interesting and well developed by Berkwitz, thus far has not been given universal acceptance. Electric shock is purely an empirical form of therapy. Several types of machines have been developed to supply the alternating current which produces convulsions by means of the application of a known potential difference between the fronto-temporal regions for a known period of time. A neat set of adjustable electrodes is applied to the frontal temporal area and a 60 cycle alternating low frequency current is used through a special timing device, allowing the current to flow 0.1 or 0.15 of a second as desired. A scale records in ohms the resistance which is found between the two terminals placed on the patient's temporal regions. One dial indicates the milliamperes, and another dial allows the desired voltage to be set. The electrodes are attached to insulated clips for ease in handling, and the terminals themselves

consist of a ball of moderately fine copper wire. The terminals are covered with a cloth sack soaked in 20 per cent saline solution. Electrode jelly, containing 20 per cent sodium chloride, is spread over the temporal contact areas. The amount of current varies from patient to patient. For the first treatment we usually set the timer at $1/10$ of a second and the voltage at 80. The milliamperage delivered is usually between 400 and 1000. As a rule the voltage has to be raised gradually as treatment progresses and frequently a



FIG 3 A Restlessness during coma B Convulsion during coma C Excitement following gastric gavage D Recovery

voltage of 120 may be required. The accompanying pictures show the sequence of events in electric convulsive therapy.

Following the passage of the current the patient may have a minor or major grand mal seizure, complete abortion of the convulsion, or a petit mal seizure. Consciousness may be lost immediately but only for a few minutes. There is an initial generalized, myotonic flexion of the body, and if not restrained the patient may assume a sitting posture momentarily. There may be only a loss of consciousness and flushing of the face with accelerated pulse

rate and shallowness of respiration. The characteristic retrograde amnesia for the seizure occurs. Petit mal responses are usually due to insufficient voltage. Some clinicians attempt to limit the application of this therapy to the minor seizure and no final conclusions are yet available as to the results of such treatment. The grand mal seizure is typically an epileptic one. Consciousness is lost immediately after the shock button is pressed and the convulsion occurs instantly or after a lapse of 30 to 60 seconds. There may be a cry. The patient will usually open his mouth and at this time a flexible



FIG 4 A Lack of apprehension prior to electric shock treatment B Muscular relaxation following Curare C Application of electrodes D Support given during electric shock convulsion

gag should be inserted. The tonic generalized contraction is associated with flushing of the face and lasts about 10 seconds, followed by the clonic phase which may be associated with involuntary loss of sphincter control, marked cyanosis of the face, and frothing at the mouth. During the seizure the eye-balls are turned upwards resembling a conjugate deviation, the pupils are dilated, the cyanosis appears to be more marked and lasts longer than with the metrazol convulsion. At the end of the fit the deep and superficial reflexes are usually absent but within a minute or two the tendon jerks are brisk with

ankle clonus, positive Babinski and Hoffman's signs. The seizure lasts from 30 to 45 seconds, following which the patient is gradually restored to consciousness and within a few minutes is able to talk drowsily although he is amnesic and confused.

Electric convulsive therapy appears to have the following advantages:

- 1 Immediate loss of consciousness associated with the painless electric shock and the complete amnesia for the whole treatment remove many of the subjectively disagreeable elements in the pharmacologically produced convulsion.

- 2 Lack of discomfort following the treatment aids in securing the needed cooperation of the patient.

- 3 It removes the inconvenience of frequent intravenous injections.

- 4 It is possible to produce both a grand mal and petit mal convulsion.

The main indications for the use of electric convulsive therapy are in the treatment of the affective reaction types. It is our policy to induce eight convulsions, two each week. There is the same tendency as seen in metrazol convulsions for improvement to be noted following the fourth or fifth seizure. Our experimental work (Whitehead, Neuburger, Rutledge and Ebaugh¹⁴) indicates that clearcut brain changes do occur which for the most part are reversible. Brain waves show the development of characteristic dysrhythmia, which in successfully treated cases gradually disappears, however, after the termination of the treatment. Curare is given intravenously in the electric shock convulsive treatments and at the present time the following routine for the prevention of fractures both in metrazol and electric shock convulsive therapy is utilized by most clinics:

- 1 The intravenous injection of curare—1 c c equal to 10 mg of the drug.
- 2 The use of a hard mattress beneath which is a hard surface. A blanket roll is placed so that it will hyperextend the dorsal spine. So-called re- in hyperextension.
3. The shoulders and hips are held firmly by nurses and attendants.
- 4 The removal of false dentures if present, and of hairpins in electric convulsive therapy.
- 5 The use of a mouth gag of resilient type.
- 6 A suitable number of assistants.

I have attempted to discuss thus far the prevalent use of the drastic therapies, insulin shock, metrazol and electric convulsive therapy in the psychoses. I hope I have emphasized the serious possibilities in the employment of these types of therapy. Deaths occur in each type of therapy as shown in table 4, obtained from the United States Public Health Service Shock Therapy Survey¹⁵.

TABLE IV
Deaths Reported for Mental Hospital Patients Receiving Shock Therapy

Type of Control	Insulin				Metrazol				Electric			
	Hos- pitals Re- port- ing*	Num- ber of Cases Treated	Deaths.		Hos- pitals Re- port- ing*	Num- ber of Cases Treated	Deaths		Hos- pitals Re- port- ing*	Num- ber of Cases Treated	Deaths	
			Num- ber	Per Cent			Num- ber	Per Cent			Num- ber	Per Cent
State Hospitals	122	2,457	121	4.9	132	28,655	47	0.2	67	5,495	3	0.05
Federal Hospitals	23	912	7	0.8	12	341	2	0.6	1	26	—	—
City and County Hospitals	7	982	8	0.8	12	1,464	—	—	8	—	—	—
Private Hospitals	46	2,607	8	0.3	46	4,221	2	0.04	29	1,186	1	0.08
Psychiatric Wards in Selected General Hospitals	6	631	3	0.5	8	492	1	0.2	8	500	—	—
Total	204	7,589	147	0.6	210	35,173	52	0.1	113	7,207	4	0.05

* Includes only hospitals reporting number of cases treated and number of deaths

SUMMARY AND CONCLUSIONS

I have presented the present day methods and therapeutic application of the drastic therapies of the psychoses by the use of pharmacological shock therapy, such as insulin and metrazol and electric convulsive therapy. The mode of action of these therapies continues unknown although there have been many theories regarding their beneficial therapeutic effect. These therapies undoubtedly serve as an ace in the hole to supplement other therapeutic methods. Insulin shock therapy may make schizophrenic patients more accessible to psychotherapy. Metrazol is now being discarded by many clinics for electric convulsive therapy which is simpler and perhaps less drastic and hard on the patient, and because, when combined with curare, the complication of fractures is eliminated. Both metrazol and electric convulsive therapy have proved to be of little benefit in the treatment of schizophrenic reactions but of considerable benefit in the treatment of the affective disorders, especially the depressive reactions. These drastic therapies were inaugurated with uncontrolled enthusiasm and, as has been true historically in other new types of therapy, have probably been made to appear more promising than is actually the case. On the other hand they have aroused tremendous interest in mental hospitals and have emphasized the importance of treatment of serious psychotic reactions, with the resultant changes in the attitude of the personnel of these institutions as well as patients and their relatives and the general public. They have presented numerous problems for research of physiological, psychological, biochemical and histopathological import and have increased further the necessary collaboration between internal medicine and psychiatry.

Whether these procedures are a permanent part of our therapeutic armamentarium or not cannot be stated at this time. Better controls, greater

uniformity, a better balanced psychotherapy with shock therapy, and better follow-up studies based on complete social, physical and psychological examinations must be made

BIBLIOGRAPHY

- 1 JESSNER, L, and RYAN, V G Shock treatment in psychiatry, 1941, Grune and Stratton, New York
- 2 U S Public Health Service Shock Survey, 1941
- 3 FROSTIG, J P Clinical observations in insulin treatment in schizophrenia preliminary report, *Am Jr Psychiat*, 1940, xcvi, 1167-1190
- 4 BRILL, H, and BINZLEY, R F Involuntary eye movements—a criterion of depth of stages of insulin coma, *Am Jr Psychiat*, 1941, xcvi, 177-181
- 5 KATZENELBOGEN, S Pharmacological shock therapy, Chapter LI, Blumer's System for Practice of Medicine
- 6 ROSS, J R, and MALZBERG, B A review of the results of the pharmacological shock therapy and the metrazol convulsive therapy in New York state, *Am Jr Psychiat*, 1939, xcvi, 297-316
- 7 ROSS, J R, ROSSMAN, J M, CLINE, W B, SCHWOERN, C J, and MALZBERG, B A two year follow up study from the New York state hospitals with some recommendations for the future, *Am Jr Psychiat*, 1941, xcvi, 1007-1023
- 8 CHENEY, C O, and CLOW, H E Prognostic factors in insulin shock therapy, *Am Jr Psychiat*, 1941, xcvi, 1029-1039
- 9 RYMER, C A, BENJAMIN, J D, and EBAUGH, F G The hypoglycemic treatment of schizophrenia A preliminary report, with particular reference to the qualitative study of remissions, *Jr Am Med Assoc*, 1937, cix, 1249-1251
- 10 PIOTROWSKI, Z A simple experimental device for prediction of the outcome of insulin treatment in schizophrenia, *Psychiat Quart*, 1940, xiv, 267-273
- 11 BENNETT, A E Curare A preventive of traumatic complications in convulsive shock therapy, *Am Jr Psychiat*, 1941, xcvi, 1040-1060
- 12 WHITEHEAD, R W, NEUBUERGER, K T, RUTLEDGE, E K, and SILCOTT, W L Pharmacologic and pathologic effects of repeated convulsant doses of metrazol, *Am Jr Med Sci*, 1940, cxcix, 352-359
- 13 CERLETTI, V, and BINI, L L'elettroshock, *Arch gen di neurol e psychiat*, 1938, xix, 266-268
- 14 WHITEHEAD, R W, NEUBUERGER, K T, RUTLEDGE, E K, and EBAUGH, F G Pathologic changes in brains of dogs given repeated electric shocks, to be published in *Am Jr Med Sci*
- 15 U S Public Health Service Shock Therapy

TUNING FORK AUSCULTATION: A TEST FOR ABDOMINAL ADHESIONS *

By B B VINCENT LYON, M D , F A C P , *Philadelphia, Pennsylvania*

It is not often that anyone wishes to open the grave and exhume the corpse to ascertain why he died an untimely death. But this is the circumstance which now confronts me. In 1922, I published ¹ a description of a new diagnostic technic. That paper attracted scant attention, for reasons now clear to me. Therefore, except for R T Ellison, who was then working in my clinic, this test lacked further study and confirmation.

The test is a combination of auscultation and vibratory percussion, and serves as a bedside addition to physical diagnosis. Its purpose is to determine, by means of a tuning fork and a stethoscope simultaneously applied to the abdomen, the likelihood of adhesions in the upper right quadrant.

Its scope is limited. It will detect adhesions involving only the stomach, duodenum, portions of the colon and the gall-bladder and liver. It will not detect adhesions between the omentum and the biliary organs, nor will it detect appendiceal, pelvic or other abdominal adhesions so far as I am now aware.

Even though thus limited to the detection of certain types of upper right quadrant adhesions, acquisition of such information is very important for the patient's welfare because it will facilitate an earlier decision as to the necessity for operation. This quick and inexpensive test will, with experience, obtain this information in a surprisingly high percentage of cases.

In 1924, Ellison ² undertook a review of 50 unselected cases in which he tabulated a comparison of the evidence of upper right quadrant adhesions as obtained by roentgen-ray with similar evidence as determined by "tuning fork auscultation." He expressed the opinion that a positive tuning fork test is strong presumptive evidence of upper right quadrant adhesions because he found it in agreement with roentgen-ray findings in 89 per cent of his cases. He considered a negative test less accurate because it agreed with roentgen-ray evidence in only 58 per cent. Ellison inferred, therefore, that roentgen-ray evidence of adhesions was more accurate than "tuning fork auscultation." None of his cases reached the operating table for final confirmation as to which technic was the more reliable.

During this long interval I have become more and more convinced of the accuracy of this simple test, as I have learned by experience to interpret it more correctly. I have, however, discarded the attempt to make the finer diagnostic distinctions as to location and degree of adhesion formation as presented in my original article. I have learned that it is wiser either to exclude all "doubtful positive" tuning fork responses or else include them in the negative group. A clean cut and consistently positive response will

* Received for publication March 25, 1942

usually mean upper right quadrant adhesions as revealed by operation irrespective of the roentgen-ray evidence to the contrary (see tables 3 and 4) ¹ Likewise, a clean cut and consistently negative response will exclude adhesions. Fine congenital adhesions, as a rule, will not give a positive response unless some degree of inflammatory adhesion formation between gall tract and stomach, duodenum or colon co-exists.

Verbrycke ² in 1940 advanced the value of combining a cholecystogram and a barium enema roentgenographic examination in determining adhesions between the hepatic flexure of the colon and the gall-bladder. A perusal of the literature from 1924 fails to reveal any further publication on this subject. So the tuning fork test died an untimely death for lack of interest and has remained buried for nearly two decades. I now propose to open the grave and reexamine the corpse in the hope that it may be found merely in a state of suspended animation and with the further hope that by presenting the following study this excellent test may be revived and may serve a larger field of usefulness.

Criteria Determined and Material Studied In preparing this article only the author's office files (1926-1939) have been consulted, and with but one objective to present unselected cases in which the tuning fork evidence is compared with the roentgen-ray evidence of upper right quadrant adhesions and then to evaluate the accuracy of each test by the actual findings at operation.

Approximately 500 case records were examined. More than four out of five were discarded for these reasons:

First, the patient was operated upon elsewhere and the operative findings were not reported to the author by the surgeon. For this reason it was necessary to exclude more than 200 cases from this statistical report.

Second, the patient had had a tuning fork appraisal but did not have a cholecystographic or progress meal roentgen-ray study. There were found to be approximately 150 such cases. Analyzing them the author found two reasons for this omission: either the patient economically was unable to undertake the expense of roentgen-ray study, or the clinical evidence including tuning fork auscultation was so clearly indicative of upper right quadrant pathologic lesions that operation was performed on this evidence alone.

Third, the patient had had either a cholecystogram, a progress meal study, or both, but the author found to his humiliation that he had not recorded (or had failed to make) a tuning fork appraisal. There were approximately 50 such cases.

Results of Material Studied Having to exclude so many cases for the foregoing reasons there remain 85 cases in which all criteria were fulfilled.

*Feldman has recently stated "The roentgen determination of adhesions in the upper right quadrant involving the gall-bladder has always been of doubtful value." Ref. FELDMAN, MAURICE. A clinical roentgenological review of the literature of 1940, pertaining to the digestive tract, *Am Jr Digest Dis*, 1941, viii, 279.

TABLE I

42 Cases in Which Both Tuning Fork Test and Roentgenological Findings Agree and Are Correct as Proved by Operation

Case	Sex Age	T F Response	Roentgen-ray Evidence for U R Q Adhesions	Operating Table Findings and Remarks
2 M L	F 30	*1, 2	Non-visualized gall-bladder, 1 large negative shadow Duodenal cap failed to fill and is irregular in outline Adhesions (?)	Biloculated g b, 1 large cholesterol stone in fundal pocket Dense adhesions between duod and both g b and liver Cholecystectomy
4 L L	M 60	*1, 2, 3, 4	Poor visualization, positive stone shadows, irregular, non-retentive duod Suggestive for duodenal and colon adhesions	Dense adhesions between g b, liver, duodenum, hepatic flexure and trans colon, 2 stones in g b Cholecystectomy with difficulty Adynamic ileus Recovery
9 G B	M 56	1	Pathologic gall-bladder and possible stones Fairly well preserved function, U R Q adhesions (?)	Large, tense, thick-walled g b, many stones, adhesions between g b and duodenum Cholecystectomy
12 A I	F 34	1, 2	G B has been previously removed Progress meal suggests U R Q adhesions	Dense adhesions between duodenum and liver Release of adhesions
20 E E	F 37	1	Cholecystitis Adhesions to duodenum No stone shadows † (Note Biliary drainage microscopy is positive for stones)	Normal appearing gall-bladder adherent to duodenum and containing 1 large stone Cholecystectomy
31 D F	F 23	Negative	Normal cholecystogram Normal progress meal	Normal g b, no stones, no adhesions Appendectomy
39 M B	F 31	Negative	G B functions to cholecystogram 1 stone shadow No evidence of adhesions Clinical diagnosis g b typhoid carrier	Small, non-adherent g b, containing 1 stone Hepatitis Cholecystectomy Patient subsequently released as typhoid carrier
40 B S	M 48	Negative	Enlarged, atonic, poorly emptying gall-bladder Stomach and duodenum are negative	Retro-peritoneal sarcoma in U R Q No adhesions Exploratory laparotomy Pt lived 18 months

* For explanation of "Tuning Fork Response" see text

† This was found true in 12 additional cases, namely nos 45, 49, 54, 58, 59, 62, 64, 66, 68, 69, 73, and 84, although the cholecystogram in most instances had failed to demonstrate the presence of stones

and in which a comparison was made of the relative accuracy of the tuning fork and roentgen-ray evidence as proved by the surgeon

Of these 85 cases, table 1 * indicates that tuning fork and roentgen-ray evidence were in agreement and found correct by the surgeon in 42 cases or 49.4 per cent Of these 42 cases the tuning fork yielded 27 positive and 15 negative tests

* Because of lack of space, details of only 32 of the 85 cases reported have been included in the tables

Table 2 indicates that the tuning fork test was correct and the roentgen-ray evidence for adhesions was incorrect as proved by the surgeon in 21 cases or 24.7 per cent. Of these there were 14 positive and seven negative tuning fork responses.

Table 3 indicates that the tuning fork test was correct as proved by operation, irrespective of the correctness of the roentgenological evidence, in 14 cases or 16.4 per cent. Of these there were eight positive and six negative tuning fork responses.

TABLE II

21 Cases in Which the Tuning Fork Test Was Correct and Roentgen-ray Evidence Was Incorrect as Proved by Operation

Case	Sex Age	T F Response	Roentgen-ray Evidence for U R Q Adhesions	Operating Table Findings and Remarks
43 S B	F 72	*1, 2, 3	Poor visualization, no stone shadows, no irregularity in outline of gall-bladder or duodenum.	Trans colon, duod., and greater curv of stomach densely adherent to g b and liver. Small thick walled g b, 6 stones in common duct. Cholecystectomy and choledochostomy.
46 F F	M 45	1	Cholecystogram is normal except suspicious for gall-stones. G I series and barium enema are normal.	Small thick walled g b, no stones, adhesions between duod. and neck of g b. Cholecystectomy. Appendectomy.
49 M D	M 56	1, 2	Non-visualized gall-bladder to dye test. No stone shadows. G I series normal.	Thick walled g b containing several stones, 1 stone in common duct, 1 stone perforated into duodenum, many adhesions between duodenum and g b. Cholecystectomy and duodenal repair.
52 F B	M 39	1	Gall-bladder normal. No stones. Perfectly acting stomach. No deformities.	Chr. cholecystitis. Stones in g b and common duct. Adhesions between g b and duod. Cholecystectomy, choledochostomy. Appendectomy.
54 L W	F 50	1, 2	Pathological g b, no stone, no evidence of adhesions. Duodenum negative. Retrocecal appendix.	Thickened g b containing 2 stones. Duodenum densely adherent to g b and liver. Cholecystectomy, appendectomy. Death on 21st p o day.
58 M S	F 27	Negative	Pathological g b to dye test, no stone shadows, adhesions between liver or gall-bladder and duodenum.	Chronic cholecystitis, 7 stones, no adhesions. Cholecystectomy.
60 W O	M 36	Negative	Pathological gall-bladder. Hepatic flexure adherent to g b. Duodenal adhesions (?).	Chronic cholecystitis. No U R Q adhesions. Cholecystectomy.
62 R S	M 39	Negative	Normal gall-bladder. Duodenal ulcer. Adhesions (?).	No duodenal ulcer. Calculous cholecystitis. 18 stones. No adhesions. Cholecystectomy.

* For explanation of "Tuning Fork Response" numerals see text

TABLE III

14 Cases in Which the Tuning Fork Test Was Correct as Proved by Operation, Irrespective of the Correctness of the Roentgen-ray Evidence

Case	Sex Age	T F Response	Roentgen-ray Evidence for U R Q Adhesions	Operating Table Evidence and Remarks
65 E T	F 67	*1, 2	Non-visualized gall-bladder No progress meal Colon di- verticulosis on barium enema	Chr cholecystitis, with dense ad- hesions between g b, liver and duodenum No stones Chole- cystectomy
67 F B	F 59	1, 3	Prepyloric ulcer No note re- garding adhesions No chole- cystogram	Chr cholecystitis with adhesions between g b, duod and trans- verse colon Pancreatitis No gastric ulcer found after gas- trotoomy Cholecystectomy
68 K M	F 61	1, 2, 3, 4	Non-visualization of g b to dye test No stones No note re- garding adhesions No prog- ress meal	Gangrenous g b adherent to col- on and duod, adhesions, also, between liver, colon and duode- num Many stones in gall- bladder Cholecystectomy, cho- ledochostomy
69 I A	F 46	1	Non-visualization to dye test No stone shadows No prog- ress meal	Tense, thick walled gall-bladder adherent to duodenum 2 stones in gall-bladder, 1 in cystic duct Cholecystectomy
71 E W	F 55	1	Cholecystogram shows nega- tive shadows in a gall-bladder preserving good function No progress meal	Thick walled gall-bladder adher- ent to duodenum and containing 6 stones Cholecystectomy
73. L L	F 19	Negative	Non-visualization to dye test No stone shadows No note regarding adhesions	Tense, distended g b, opaque walls, 4 stones in g b, 2 in cystic duct, 4 in common duct Chole- cystectomy, choledochostomy Chemistry of stones 95% chol- esterin, 5% calcium bilirubi- nate
74 R R	M 52	Negative	Retrocecal appendix Sigmoid colon adherent to cecum No reference to U R Q adhesions	No U R Q adhesions Normal g b Appendix not found after 90 minutes' search Sigmoid colon was not adherent to ce- cum
76 F C	M 39	Negative	Pathological g b, normal du- denum, non-visualized appen- dix No note regarding ad- hesions	No U R Q or other adhesions G B visibly and palpably nor- mal Appendix contained fe- calith Appendectomy

* For explanation of "Tuning Fork Response" numerals see text

Table 4 indicates that the tuning fork was incorrect as proved by operation, irrespective of the correctness of the roentgenological evidence, in eight cases or 9.4 per cent. Of these the tuning fork yielded five positive and three negative tests.

In the aggregate, therefore, the tuning fork test was proved correct in 77 cases or 90 per cent. The incidence of positive to negative tuning fork

TABLE IV

8 Cases in Which the Tuning Fork Test Was Incorrect as Proved by Operation, Irrespective of the Correctness of the Roentgenological Evidence

Case	Sex Age	T F Response	Roentgen-ray Evidence for U R Q Adhesions	Operating Table Findings and Remarks
78 M D	F 29	*1	Normal cholecystographic response No progress meal	Surgeon reports "Pathological gall-bladder No adhesions" Cholecystectomy.
79 S C	F 48	1, 2	Pathological, greatly enlarged gall-bladder No note regarding adhesions	Surgeon reports "G B enlarged, slightly thickened, non-adherent, contained no stones" Cholecystectomy
80 M F	F 47	1, 2	Normal Graham test response. No progress meal No irregularity in g b outline	Surgeon reports "G B perfectly normal No adhesions No stones No abdominal pathology Retrocecal appendix, but not in bad condition" Appendectomy
81 J T	M 66	1, 2	Pyloric carcinoma, duodenal adhesions, pathological gall-bladder	Carc of pylorus Normal g b No adhesions Post gastrojejunostomy Death in 2 days
82 H K	F 43	1	"No roentgen-ray evidence of pathology of stomach or duodenum except for duodenal adhesions to a definitely pathological g b which may contain stones, fixation of cecum"	Surgeon reports "We felt this pt had g b disease partially based on our roentgen-ray dept report of a deformity of the stomach, but at operation the g b, stomach and duodenum were normal" Closure
83 E M	F 49	1, 2	Pathological cholecystogram Suggestive evidence for U R Q adhesions involving gall-bladder	Thick walled, non-adherent g b, no stones, dense adhesions between transverse colon and abdominal wall Cholecystectomy
84. F J	M 34	Negative	Poorly visualized g b, no stone shadows, normal progress meal response	G B firmly adherent to duod and containing several stones, 2 duodenal diverticula Cholecystectomy
85 M K	F 64	Negative	G B not visualized to dye test Faint mottling to suggest stones in gall-bladder and in cystic duct	Surgeon reports "G B shows chronic inflamed and thickened walls It contained several calculi and was adherent to adjacent structures" (Note surgeon did not specify to what structures) Cholecystectomy Appendectomy

* For explanation of "Tuning Fork Response" numerals see text

responses was 5 4 to 3 1 Both varieties were equally accurate, percentage wise

COMMENT

In these tables the tuning fork response is entered as a numerical figure according to the following interpretative code.

Numeral I suggests adhesions between the gall-bladder and the pyloro-duodenal segment, because the T F response was positive between the right subcostal margin and the epigastrium (see technic of performing test)

Numeral II suggests adhesions between the liver and the pyloro-duodenal segment because the T F response was positive between the liver and the epigastrium

Numeral III suggests adhesions between the gall-bladder and the colon (usually the hepatic flexure) because the T F response was positive between the right subcostal margin and the cecum

Numeral IV suggests adhesions between the liver and the colon, because the T F response was positive between the liver and the cecum

In examining these tables, the reader will also note that the roentgen-ray evidence and the operating table findings are reported only in abbreviated summary in order to save space. In doubtful cases, wherever possible, the author has thrown the weight of evidence against his test and in favor of roentgen-ray

In tables 3 and 4 the reader will note the author's inability correctly to appraise the roentgen-ray evidence without appearing biased. A study of these tables will explain why

In order further to conserve space, the author has reduced, in the text, tables 1, 2 and 3 to a report of eight cases which represents a sampling of the total number in each group

Equipment for Tuning Fork Auscultation The equipment necessary for this test is simple and inexpensive. The examiner, in addition to possessing good hearing sensitive to tone, requires only a stethoscope and a tuning fork

The author has found that a bell type stethoscope 26 inches over all is desirable, for reasons subsequently stated. This means approximately 18 inches of rubber tubing, the last six inches of which should be a single tube

The tuning fork should be a large size G sharp of 410 vibrations. The standard dimensions of this fork are 7 inches over all, 4.5 inches from tip of prong to fork, and 2.5 inches from fork to tip of stem. Each prong is $\frac{7}{16}$ inch deep and $\frac{1}{16}$ inch wide. The author has found by experience that the stem of this standard fork is too short to be held comfortably without some portion of the fingers or hand touching the abdomen. Such contact will give false readings because of surface conduction of sound. To overcome this the author has lengthened the stem, by welding, to an over all of 8.5 inches

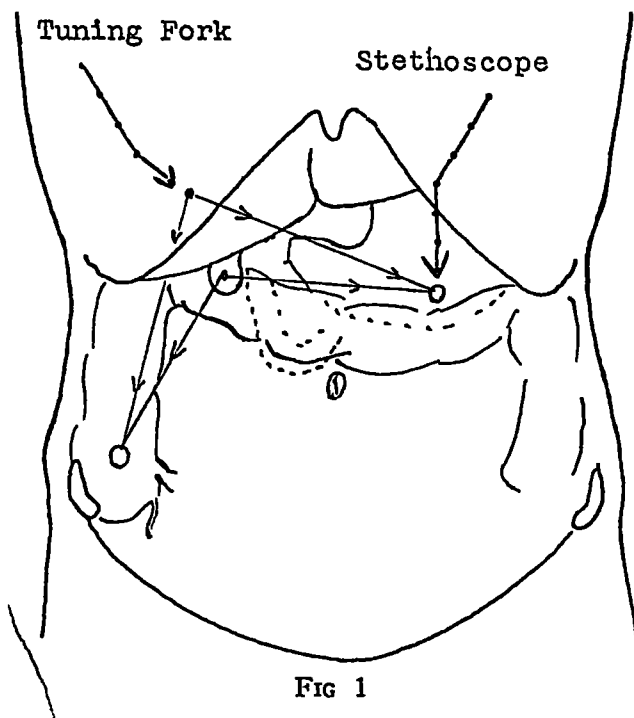
The extra long rubber tubing on the stethoscope is also important because it permits the examiner, when standing at the left side of the recumbent patient, to have sufficient length comfortably to transfer the bell of the stethoscope from the patient's left epigastric region to his lower right quadrant

General Principle Underlying Test The underlying principle of the test is the conduction of or transmission of a tuning fork note from one hollow

organ to another hollow organ, for instance from gall-bladder to stomach or duodenum, or from a solid organ to a hollow organ, for instance from the liver to the colon. This is possible, however, only if the two organs are in permanently close relationship to each other, that is bound to each other by adhesions.

Ellison² discusses the mechanics or physics of the test as follows: "When adhesions unite the pyloro-duodenal segment to the under surface of the liver or to other structures, such as the gall-bladder, which are in anatomic union with the liver, there is formed a continuity of anatomic structure between the liver and the walls of the stomach. If now the stem of the vibrating tuning fork is placed over the liver, the vibrations are transmitted directly from that organ to the walls of the stomach. The air bubble, which in the dorsal position lies in the left hypochondrium, acts as a resonator for the vibrations, amplifying them so that they can be heard by the overlying stethoscope. Mere apposition of structures does not produce the same sharp clear note, because the vibrations are dampened in passing from one structure to the other."

Technic of Performing the Test The patient lies comfortably and evenly on his back. The examiner stands at the left side of the patient. The examiner places the bell of his stethoscope over the patient's epigastrium so that it occupies a portion of the topographical region of the patient's stomach. (See illustration.)



The examiner now smartly taps the tuning fork (preferably on his heel) and places its butt or stem close to the bell of the stethoscope. The musical note which the examiner will hear will be that given off by the patient's stomach. This musical note hereafter will be referred to as the 'gastric note'.

By means of "tuning fork auscultation" the examiner can then rapidly map out the size, shape and position of the stomach much the same as if he were attempting to do so by ordinary percussion or by auscultatory percussion. To do this the examiner first brings the stem of the vibrating tuning fork upwards, inch by inch, from various points in the lower left quadrant and towards the bell of the stethoscope. The reappearance of the 'gastric note,' clear and distinct, will indicate that the stem of the tuning fork has reached the lower border of the stomach. Second, the lateral border of the greater curvature can similarly be determined by bringing the stem of the vibrating tuning fork inwards from the splenic region. Third, the smaller area of the lesser curvature which lies below the costal margin can be best delineated by bringing the vibrating tuning fork from the mid right sub-costal region inwards toward the stomach. As each portion of the stomach is reached the same clear cut tuning fork 'gastric note' will reappear. The pyloro-duodenal segment, representing some portion of the pyloric region and the duodenum, will also be found to lie within the third zone above described for outlining the lesser curvature. These are normal or negative tuning fork responses because they outline the average normal boundaries of the normal stomach.

Let me now discuss, equally briefly, the abnormal or positive tuning fork responses. It would be abnormal, and pathological in the sense of suggesting the presence of adhesions, if the examiner were to find that the clear cut 'gastric note' could be heard well beyond the normal boundaries of the stomach.* To be more specific as to possible adhesion formation and its location, there are four principal groups which the examiner should seek to identify: first, adhesions between the gall-bladder and the stomach or duodenum (the pyloro-duodenal segment), second, adhesions between the liver and the pyloro-duodenal segment, third, adhesions between the gall-bladder and the colon, fourth, adhesions between the liver and the colon.

Group I Determination of adhesions between the gall-bladder and the pyloro-duodenal segment

Using the same technic as just described for outlining the third zone or lesser curvature area, when the examiner can hear the 'gastric note' clearly and loudly below the right costal margin and laterally as far as or beyond the tenth rib, this should be considered abnormal. This would be presumptive evidence that some portion of the gall-bladder and some portion of the pyloro-duodenal segment are adherent. This notation of the tenth rib is arbitrary. It will not, of course, apply to a gall-bladder abnormally situated close to the spinal column as frequently occurs in a ptotic subject and is often thus demonstrable by cholecystogram.

Group II Determination of adhesions between the liver and the pyloro-duodenal segment

The examiner continues to keep the bell of the stethoscope over the stomach area in the left epigastrium, but now varies the technic by placing

* Ptois and atony (dilatation) of the stomach might also be suggested as abnormalities

the stem of the vibrating tuning fork over the liver, that is above the right costal margin. In certain cases the examiner will find that the 'gastric note' will be transmitted equally clearly and loudly from this area. In such cases this would be presumptive evidence that some portion of the liver and some portion of the stomach or duodenum are adherent to each other. Otherwise it should not be possible to transmit tuning fork vibrations from or through a solid organ (liver) to a hollow organ (stomach). The wider the area over the liver from which such vibrations can be transmitted, the more dense and widespread have been the adhesions when visualized at operation. However, there are two exceptions. When the liver is considerably enlarged, especially its left lobe, this interpretation of the test may be inaccurate because of direct sound conduction. Second, the examiner must avoid stretching the skin between bell of stethoscope and stem of tuning fork, since this will produce surface conduction of sound.

Groups III and IV Determination of adhesions between gall-bladder and colon, and between liver and colon.

In the foregoing description of determining adhesions between the gall-bladder or liver and the pyloro-duodenal segment there is one major error that must be eliminated. This arises from the fact that in many cases the middle third and left third of the transverse colon may lie in juxtaposition to the stomach. Therefore, with the bell of the stethoscope placed over the stomach, as I have already described, it may also lie over some portion of the transverse colon. It would do so in non-coloptotic patients. With this in mind, and with the vibrating stem of the tuning fork alternately placed below and above the right costal margin, let us now suppose that in a given patient the examiner clearly hears this presumable 'gastric note' transmitted from the gall-bladder or liver region to the epigastric region over which he has placed his stethoscope. Why could not this be a note transmitted from the gall-bladder or liver to the *colon* instead of to the stomach?

Fortunately it is quite simple to decide whether the musical note thus heard is solely colonic and not gastric and the examiner proceeds as follows. If he places the bell of the stethoscope over the first portion of the ascending colon (that is in a position slightly above and to the right of the classical McBurney point) the tuning fork note given off from that region obviously should emanate from the colon rather than from the stomach. Next, if he places the stem of the vibrating tuning fork alternately under and over the right costal margin a definitely positive response will strongly suggest that adhesions are present between some portion of the colon (usually the hepatic flexure) and either the gall-bladder or the liver.

But a second possible error of interpretation remains to be eliminated. In the event that there are adhesions between gall-bladder and liver to *both* the pyloro-duodenal segment and the colon, why could not the note which the examiner has so clearly heard be transmitted to both stomach and colon? This, too, is easy to differentiate by the following maneuver. With the vibrating tuning fork placed alternately below and above the right costal

margin the examiner first auscultates over the epigastric region and then quickly transfers the bell of the stethoscope to the ascending colon near the McBurney point. If the musical tuning fork note is heard with equal clarity and definite positiveness at *both* positions this would be presumptive evidence that adhesions exist between the biliary tract and both the pyloro-duodenal segment and the colon. However, if the musical note is clearly heard in the epigastrium only, the possibility of adhesions between colon and biliary tract is thereby eliminated, and vice versa if heard only in the region of McBurney's point.

In the average normal abdomen the distance, topographically, between the gall-bladder and the indicated position of the stethoscope over the stomach (see illustration) is approximately the same as the distance between the gall-bladder and the cecum. This would make the distance between the gall-bladder and stomach, the gall-bladder and cecum, and the stomach and cecum equidistant like a triangle. Therefore, no error in interpreting the intensity of the tuning fork note should occur because the stethoscope might be nearer to it in one location than in the other.

Caution and Advice to Beginners Changing the bell of the stethoscope from one position to the other must be done rapidly and the examiner must remember that the intensity of the sound is constantly lessening with each instant of elapsed time and that this factor may modify his interpretation. Another counter-check may be made by revibrating the tuning fork each time the position of the bell of the stethoscope is altered. The latter may be better technic for the beginner who by practice, supplemented by operating table observation, will quickly learn what may have caused a misinterpretation of his findings and thus will teach him how to guard against repeating his mistake.

Tuning fork auscultation for adhesions is not an exact test that can be measured by a graph or a mathematical or chemical formula. It has a large degree of "personal equation" similar to that required in expertly palpating the abdomen, and much greater than that required accurately to record a blood pressure ratio or to do a complete blood count. It is a test whose accuracy will increase with experience cross checked by operating table inspection.

There are several errors in technic to be avoided. While applying the bell of the stethoscope and the stem of the tuning fork to the abdomen the examiner should push them toward each other. This relaxes the skin. Do not pull them away from each other. This will stretch the skin and will thus produce a "false positive" by surface conduction of sound. This is a common error and can be easily proved by alternately relaxing and stretching the skin between stethoscope and tuning fork.

A second and similar error will occur if the fingers holding either instrument are allowed to touch the abdomen. It is to guard against this that the lengthened tuning fork stem and lengthened stethoscope rubber are required, the measurements of which I have recorded earlier.

A third error will occur if the examiner stands at the right of the recumbent patient. In this position the prongs of the tuning fork will come too close to the tubing of the stethoscope and thus falsely transmit the sound. Try it and see.

A fourth and important error is one of omission. The test should be repeated at least twice and preferably on different days, and it should always yield the same result—a clean cut positive or a clean cut negative. This will guard against a “false positive” being produced by a peristaltic wave carrying the duodenum or the hepatic flexure of the colon, for example, into juxtaposition with the gall-bladder at the very instant the examiner makes the test.

Should the patient happen to have an intubated duodenal tube in stomach or duodenum at the time “tuning fork auscultation” is being made the positiveness of the test will be increased by injecting through the tube one or two ounces of air. This appears to act as a sounding board.

Let me again remind the beginner that he will make fewer errors if he goes on record with only clean cut positive or clean cut negative responses. There are intermediate readings that can be made with experience, but it is better for the reader to learn them himself than to be told.

Any surgeon with an active abdominal service can quickly check for himself the accuracy of this test by adding it to his routine examination of all patients whose abdomens he proposes to open, provided he plans visibly to inspect the upper right quadrant. Intraabdominal palpation of finer adhesions is often unreliable. Visible inspection will guard against this error decreasing the accuracy of tuning fork auscultation. With practice the test can be done readily in five minutes. It cannot be hoped that a beginner can achieve such a high percentage of accuracy with this test in his first group of cases any more than such accuracy can be expected in the hands of an inexperienced roentgenographer or of a novice with any new tool.

The accidental manner in which the author stumbled upon this test in 1911 was described in his original article.

COMMENT

The author has noted three different points of view regarding the value of this test.

First, that of the expert roentgenographer who is meticulous about every detail of his work. Such a one has a sufficiently competitive spirit to make him jealous of any one who can challenge the diagnostic accuracy of himself and his apparatus. For 15 years or longer Dr. Willis F. Manges, Professor of Roentgenology in the Jefferson Medical College, and I had been in friendly competition in detecting upper right quadrant adhesions. Prior to his untimely death (1936) Dr. Manges told me that, according to his score

card, my tuning fork test was 14 per cent more accurate than his beloved machine

Second, there has been the surprised attitude of the operating surgeon when he has confirmed my preoperative diagnosis of upper right quadrant adhesions or their absence. Especially was this the case when my tuning fork diagnosis differed from the roentgenologist's report upon the accuracy of which he had come to rely.

Third, there was the general attitude of indifference on the part of the occasional doctor who was apt to say "Well, suppose the patient does have upper right quadrant adhesions. What of it? How does it help you or the patient if you can recognize them preoperatively?"

I reply that it has helped me or the patient in three ways.

It has helped me more accurately to select for surgery the patient who requires surgery. The preoperative knowledge that adhesions involving the upper right quadrant actually exist is important because adhesion formation so frequently accompanies chronic gall-bladder disease and chronic gastroduodenal disease. This is the kind of disease that will be best eradicated or controlled by appropriate and skillful surgery. This test is more accurate in securing such information than is roentgen-ray, and far more so than intuitional guesswork.

Second, such information is important to me and to my patient because whenever adhesions are cut they are apt to reform. This is a *bête noir* to the surgeon, but a far greater one to the patient because their reformation tends to produce postoperative morbidity and suffering. Remembering this, the doctor is in a better position to plan the immediate postoperative care (narcotics, diet step-up, duration of hospital stay), and the longer 'follow up' with a skill personalized to his knowledge of his patient and his disease.

Third, such information is vastly important to the patient and to his attending physician because the presence of adhesions greatly increases the technical difficulties of the operation. This imposes a responsibility upon the physician, and it should equally influence the 'occasional' surgeon, to make sure that such a patient gets the highest surgical skill that is available. All of the patients in this report were operated upon by surgeons of unquestioned skill and experience in this field of surgery. Even so, it still shocks me out of my complacency to recall so many patients who failed to recover. The shock of such a death to the family and to the referring physician is not so great if the patient is found suffering from cancer. This was found present in six of the 11 deaths and raised the total mortality to 12.9 per cent. The mortality in the non-cancer patients was thus reduced to 6.3 per cent. Surely, even such a mortality will be considered too high. And when I state that the surgeons who operated upon the large majority of this series of patients were Professors of Surgery, that fact alone emphasizes the seriousness of complicated upper right quadrant disease and suggests that a higher mortality would result in less skillful and experienced hands.

SUMMARY AND CONCLUSIONS

1 A diagnostic technic is described for determining the presence of adhesions in the upper right quadrant of the abdomen

2 This test is simple, inexpensive and accurate. It is called "Tuning fork auscultation—a test for abdominal adhesions." It requires only a stethoscope, a tuning fork, good hearing and adequate experience.

3 The author presents 85 cases in which tuning fork auscultation was compared with roentgen-ray evidence of upper right quadrant adhesions and was then proved correct or incorrect by operating table inspection.

4 In this series of cases the test was found to be 90 per cent accurate, whereas roentgen-ray evidence was something less than 65 per cent accurate.

5 The method of performance, as well as the errors in technic, are fully described.

BIBLIOGRAPHY

- 1 LYON, B B VINCENT A clinical method of determining adhesions between the stomach and gall tract, *Surg, Gynec and Obst*, 1922, xxv, 232
- 2 ELLISON, R T Adhesions in the upper right abdomen, *Arch Int Med*, 1924, xxxiv, 721
- 3 VERBRYCKE, J R Adhesions of cholecystohepatic flexure new syndrome with specific test, *Jr Am Med. Assoc*, 1940, cxiv, 314

ALLERGY TO INJECTABLE LIVER EXTRACTS; CLINICAL AND IMMUNOLOGICAL OBSERVATIONS *

By SAMUEL M. FEINBERG, M.D., F.A.C.P., HOWARD L. ALT, M.D., and
RICHARD H. YOUNG, M.D., F.A.C.P., *Chicago, Illinois*

THE last two or three decades have witnessed tremendous and far-reaching advances in therapeutics, in many instances specific in character. This has been particularly true in the case of highly potent injectable substances such as immune sera, hormones, vitamins, and such specific factors as the antianemic liver fraction. With the older types of materials allergic reactions such as asthma, urticaria or serum sickness were obtained and were not unexpected, since they contained a considerable quantity of the animal proteins which were regarded as an essential feature of the mechanism of the reaction. Later, it was shown that even such a pure substance as crystalline insulin is capable of producing allergic reactions, acting as an antigen irrespective of the animal source.

It is our purpose here to call attention to the importance and significance of reactions to one type of injectable substance, i.e., liver extract. Since the introduction of parenteral liver therapy in 1932, 29 authentic instances of allergic reactions to liver injections have been reported. Considering the number of persons who have received such injections the impression is created that these reactions are infrequent and unimportant. In view of the fact that we have had the opportunity of observing and studying eight patients with definitely corroborated findings of liver allergy and that five of these have come from one clinic (the Hematology Clinic of Northwestern University Medical School), it is not unlikely that this problem is more common and widespread than the medical literature depicts. The majority of the case reports do not give evidence of the necessary observations in order to ascertain the nature of this type of allergy, its course and its significance. It is because of these considerations that we are prompted at this time to record the findings and studies on this group of individuals.

CASE REPORTS

Case 1 L. H., a 65 year old woman, was seen in the Hematology Clinic in the autumn of 1937, where a diagnosis of pernicious anemia was made. One c.c. of Reticulogen (Lilly) was injected on October 23 and on November 13. On December 11, 1937, fifteen minutes following the third injection of liver extract, she began to have itching of the palms of the hands and soles of the feet. This was soon followed by cough, dyspnea and wheezing. Epinephrine hypodermically caused a prompt subsidence of the attack. The subsequent injection of liver extract induced a

*Received for publication February 5, 1942

From the Division of Allergy and the Hematology Clinic, Department of Medicine, Northwestern University Medical School

similar reaction On February 16, 1938, she was given one-half cubic centimeter of Reticulogen intramuscularly, which was followed by a severe attack of generalized urticaria, edema of the eyes and lips, and dyspnea with blood-stained sputum

On February 19, 1938, she was seen in the Allergy Clinic In addition to the aforementioned story she gave a history of urticaria and asthma of several years' duration as well as a description of symptoms of allergic rhinitis A son had hay fever To substantiate her chronic allergic complaints, routine cutaneous tests disclosed several marked reactions, particularly to cattle hair, hog hair and house dust Cutaneous tests were made with 10 commercial injectable liver extracts, with positive reactions to all but one By the intracutaneous method all antianemic liver preparations reacted, the reactions being obtained in as high as 1:100,000 dilutions with some of the products Most of these liver extracts were obtained from livers of beef or hog origin A preparation of liver extract obtained from the horse also gave a positive reaction Because of the implication that we might be dealing with a special antigen residing in a fraction of the liver which is common to all mammalian livers and because of the theoretical interest that is attached to the possibility of auto-antigens, it was thought advisable to investigate the reactivity of the antianemic fraction of human liver Such a preparation was made and resulted in absolutely negative reactions, whereas extracts made from beef and hog liver by the same method gave positive reactions

Tests made with the pressed juice of the pork and beef liver or with protein fractions in varying dilutions gave positive reactions, but required higher concentrations to produce them Because of the possibility that the specific antigen might be due to parasites which infest the cow and the hog, tests were made with extracts of ascaris and tapeworm, with negative results One-tenth cc of the serum from this patient was injected intracutaneously in several skin sites of a non-atopic individual Subsequently these sites were tested with anti-pernicious anemia liver fractions and reactions were obtained with dilutions as high as 1:1,000

For a time the patient was given liver orally The response being poor, it was thought advisable to attempt to immunize her sufficiently to be able to resume parenteral therapy This was begun in October 1939, and continued irregularly until May 17, 1941, when a dose of 0.8 cc of the 1:100 extract was reached During the course of these immunizing injections the patient had many marked local reactions and several mild constitutional allergic reactions Two intensive courses of histaminase orally did not alter the titer of skin response At the last testing (August 19, 1941) her skin tests showed reactions to practically as high dilutions as they did three and a half years before

Case 2 A Q, a 52 year old woman, was seen in the Hematology Clinic in October 1938, where a diagnosis of pernicious anemia was made She had 14 injections of liver extract (3 cc Lilly's, 1 cc = 2 USP units), the first ones being given frequently and the later ones every three weeks A few minutes following the fifteenth injection, on May 13, 1939, she had generalized urticaria and vomiting On July 15, 1939, she had a moderate reaction from one-fourth cubic centimeter of the extract

She was seen in the Allergy Clinic on August 22, 1939 No history of atopic disease in the patient or in the family was elicited All the usual routine, cutaneous tests were negative Marked cutaneous and intracutaneous reactions were obtained with several brands of injectable liver extracts in dilutions up to 1:1,000 No reactions were obtained with horse liver in concentration as high as 1:10 The human liver preparation gave a negative response Liver juice, liver protein fractions, muscle protein fractions, and protein fractions from kidney and stomach did not produce positive reactions The parasite extracts did not react Passive transfer disclosed the presence of reagin, reactions being obtained with 1:10 dilution of liver extracts

On August 19, 1939, immunization was begun with Reticulogen and after several months a dose of 5 cc of the undiluted extract was reached. This dose was continued to August 24, 1940. During the process of immunization one systemic reaction occurred. Tests repeated on December 16, 1939, still showed marked reactions.

Case 3 M T, a 68 year old man, was admitted to the Hematology Clinic on November 15, 1939 where a diagnosis of pernicious anemia was made. He received 10 injections of liver extract in a period of about four months, most of the treatments being administered at two week intervals. His first injections were of Lilly's concentrated extract (1 cc = 15 U S P units) and the later injections were of Reticulogen (1 cc = 20 U S P units). On May 18, 1940, a few minutes after his eleventh injection of liver extract, he complained of itching in the ears and palms of the hand and tightness in the chest. He was seen in the Allergy Clinic on May 28, where he gave an additional history of autumnal hay fever of 20 years' duration. Of all the routine skin tests made ragweed pollens were the only positive reactors. Several injectable liver extracts gave definite cutaneous reactions. The horse liver extract also gave a positive response. Protein fractions of beef and pork liver as well as protein fractions of the muscle tissue of these animals failed to give reactions. Tests made with the injectable liver extracts were still strongly positive six months later. On January 14, 1941, one-half cc of an outdated Lederle liver extract (1 cc = 15 U S P units) was administered. A constitutional reaction resulted. On January 18, 1941, a reaction was precipitated by 0.1 cc of the same extract. The patient has not returned for observation since that time.

Case 4 P P, a 43 year old male, a private patient, had been taking injections of Lederle's liver extract (1 cc = 15 U S P units) at three week intervals for a period of 13 months for pernicious anemia. The last injection resulted in a generalized urticaria occurring within five minutes. An inquiry into his past history disclosed the fact that he had had a siege of urticaria 10 years previously. Tests were begun on December 12, 1939. All commercial liver extracts gave strong reactions. This included preparations of beef, pork and horse origin. The protein extracts of the beef and pork liver, as well as the protein extracts of the beef and pork muscle gave negative responses. The extracts of ascaris and tapeworm did not react. In spite of the skin reactions he was able to tolerate continued injections of a special beef liver extract (Lederle, 1 cc = 15 U S P units).

Case 5 W H, a 46 year old male, was seen in the Hematology Clinic in July 1940 where a diagnosis of pernicious anemia was made. After a series of injections of Reticulogen consisting of daily small doses followed by three injections at intervals of three weeks, a reaction occurred on November 14, following an injection of 1 cc of the preparation. The symptoms consisted of itching of the hands and thighs, marked weakness and nausea. He was seen in the Allergy Clinic on December 21. There was no personal or family history of atopy. Positive cutaneous and intracutaneous reactions were obtained with several commercial liver preparations, which included beef, pork and horse sources. The pressed juices of pork and beef liver reacted slightly. The proteins of pork and beef muscle gave no reactions. Reagents were obtained from the serum but precipitins were not found.

Following an interval of six weeks after his last therapeutic injection of liver extract, the treatments were continued without any constitutional effects.

Case 6 F E, a 47 year old man, developed an itching rash after several months of liver injections (various preparations) for pernicious anemia. There was no history of atopy. Moderate positive cutaneous and intracutaneous reactions to several liver extracts were obtained. Tests with liver and muscle proteins were negative. This patient was able to continue with injections without further reaction.

Case 7 M S, a 20 year old male, had been under observation in the Dermatology Clinic for a stubborn acne. A fraction obtained from an anti-pernicious

anemia liver extract and from crude liver extract (designated A-1) and apparently containing no chemically demonstrable protein was given intramuscularly as a therapeutic procedure. After one series of treatments six months elapsed before the second series was begun. The first reaction occurred on the second injection of the second series, and consisted of urticaria and faintness. A similar reaction occurred on the third injection and following the fourth injection a severe attack of asthma ensued. Treatments were then discontinued and allergic studies were begun.

A history elicited the fact that the young man had had a perennial rhinitis for several years and also had what was probably midsummer and fall hay fever. Routine skin tests disclosed definite reactions to grass and ragweed pollens and to house dust. Positive cutaneous and intracutaneous reactions were obtained with numerous commercial preparations of liver extracts as well as with the special fraction with which he was treated. With some of the materials intracutaneous reactions were obtained with dilutions as high as 1:1,000,000. Lesser reactions were obtained with the horse liver preparation. The pressed liver juice and the protein fractions gave reactions but in much lower concentration than with the non-protein fractions. Muscle and other organ protein fractions as well as the parasite extracts gave negative reactions. Reagins were demonstrated with 1:1,000 dilution of some of the liver antigens. Precipitins could not be demonstrated. Tests have been repeated over a period of eight months, the last made (July 15, 1941) showed no appreciable difference in the intensity of the skin reaction.

Case 8 J. P., a 68 year old woman, was under the care of Dr. Paul Shallenberger, for an anemia of undetermined nature. She had been receiving injections of liver extract (Reticulogen, 0.5 cc) at first weekly and then every 10 days. About two minutes following the sixteenth injection there ensued a reaction consisting of itching of the hands and feet, swelling of the tongue and throat and dyspnea, apparently without wheezing. The patient was referred to us for allergic tests which were made about three weeks after the constitutional reaction. Cutaneous tests showed decided sensitivity to several commercial brands of injectable liver extracts (beef, pork and horse). The beef liver extract and horse liver extract reacted less than the hog liver preparation. The protein-rich pork and beef liver juices, as well as the muscle preparations of these animals failed to react.

ANALYSIS OF CASES

Relation to Atopy The question arises as to whether there is a relationship between this type of induced allergy and the presence of atopy (asthma, hay fever, etc.) in the patient. Harten and Walzer,¹ in their thorough review, find that in the total of 28 cases reported in the literature, seven were frankly atopic persons. There is the possibility, of course, that some of the others may have also been atopic and that not every author has seriously inquired about the presence of atopy or has failed to record it. In our series of eight cases, three had long established chronic atopic manifestations, and another had some recurring urticaria. It may not be entirely insignificant that these three frankly atopic persons have not been able to tolerate injections of full doses of liver extract even after long intervals or after prolonged periods of "desensitization."

Liver Injections Preceding Allergy In all instances the reactions followed injections which were previously tolerated without any difficulty. The number of such injections preceding the first allergic episode varied from

two to about 15. A study of the original case records would indicate that a long interval between injections (three weeks), or a long period between series of injections favors the establishment of sensitization. In none of these patients were reactions initiated while they were receiving injections at intervals of one week or less.

Clinical Manifestations Asthmatic reactions occurred in about half of the patients. Either itching and flushing of the skin or some form of urticaria or angioneurotic edema was manifested in practically all patients. Nausea, weakness and faintness were common complaints. As a matter of fact, the different allergic manifestations occurred often at different times in the same individual when repeated reactions were produced. There was a tendency for the lighter reactions to occur first and for the more severe manifestation to appear on the repetition of the injections. In the approximate order of increasing severity these manifestations consisted of itching of the skin, particularly of the palms of the hands, or flushing of the face, nausea and slight faintness, generalized urticaria and angioneurotic edema, asthma, and generalized reactions. Anaphylactic shock has been described by others.

Skin Tests with Commercial Antianemic Liver Fractions In the reports included in the review of Harten and Walzer, 11 patients had been tested intracutaneously, with positive reactions in nine. In our series all patients gave the immediate whealing type of cutaneous (scratch) and intracutaneous reaction with the commercially prepared injectable liver extracts. A fairly large series of persons with other allergy gave negative reactions to these extracts. One patient who had a very mild constitutional reaction and who was able to continue with his liver injections failed to give positive scratch reactions but gave a fairly strong reaction to the 1/100 extracts intracutaneously. His case is not included in this series. The volume of the intracutaneous injections never exceeded 0.02 c.c. Positive reactions intracutaneously were obtained in different patients in dilutions ranging from 1/100 to 1/1,000,000. In performing these tests a variety of commercial brands of liver extract was used and although positive reactions were obtained with essentially all of them there was some variation in the titer of the reaction. In all instances both the beef and pork liver extracts gave positive tests. The horse liver extract gave positive reactions in all cases tested but one, although the reactions to this preparation were usually weaker. No delayed, or alarming immediate local or general effects such as have been described previously followed the tests, presumably because very strong concentrations were not used when weaker ones gave definite reactions.

Skin Tests with Specially Prepared Extracts A human liver extract was prepared in accordance with a standard method for separating the anti-pernicious anemia principle. This extract gave entirely negative reactions in two patients who were strongly sensitive to other liver extracts. In order to ascertain whether we were dealing with an organ specificity we made tests

with other liver fractions. The proteins precipitated from the macerated liver, and prepared as protein antigens are usually prepared for routine allergic tests, gave negative reactions for the most part. The same was true of the pressed liver juice, which, though extremely rich in proteins, gave little reaction on these patients. When positive tests were obtained with these products they were evident only in comparatively high concentrations. It was apparent that the preparations containing tremendous quantities of proteins had very small quantities, if any, of the antigen in question, whereas the preparations which failed to disclose any protein by chemical tests (some of the commercial liver extracts) had high concentrations of the antigen. The only patient who was an exception to this observation was Case 1 who reacted to the protein fractions in fairly high dilution. The nature of her allergy is further complicated by the fact that she gave strong reactions to cow and hog dander. It may be that in her case several separate allergies are involved, some previously existing and the others induced.

In all instances protein extracts of the muscle (meat) of beef and hog gave negative reactions. This is in conformity with previous reports^{2, 5, 6, 7}. Protein extracts of kidney and stomach were tested in three patients and the only positive reactions were obtained in Case 1. Fractions of these organs prepared according to the method employed in preparing the antianemic fraction of liver gave moderately positive tests in Case 1 and negative in Case 4.

In four patients tests were made with extracts of ascaris and tapeworm. This was done because of the remote possibility that the curiously behaving liver antigen might originate from the infestation of some of the animals with these parasites. Negative tests were obtained in all.

Specific Antibodies Of the patients reviewed by Harten and Walzer, eight who had direct positive skin reactions were tested by the indirect method (passive transfer) also. Of these, seven showed passively sensitizing antibodies^{2, 4, 5, 6, 7, 8, 9}. In our series four patients were tested in this manner and all of them showed reagins specific for liver extract. That is to be expected, since a true immediate type of allergic reaction always displays passively transferable reagins if the titer of reactivity is sufficiently high. The sera of two patients were tested for precipitins to liver extract but no appreciable titer was found in either.

Clinical and Immunologic Course The clinical course of these patients is somewhat varied. In four of these cases full therapeutic doses of liver extract could not be administered without reaction, after an interval of several months to three and one-half years following the initial reaction. In another (case 8) it is too early to say whether liver would be tolerated in the future, since the allergic reaction has occurred only recently. However, in view of the violent and serious nature of the reaction, such an eventuality remains in doubt. The three remaining cases were able to resume liver injections without any interfering reactions. The status of these patients who have been able to continue with liver injections is of

interest Cases 5 and 6 had the mildest constitutional reactions and skin reactions of low degree Both were able to continue with the standard liver extracts Case 4 was changed to an extract made from beef liver and he has been able to tolerate this material On his tests he had shown strong reactions to both pork and beef liver, the latter, however, being less in intensity It is possible that this difference was of sufficient degree to enable him to tolerate the special beef liver extract

TABLE I
Clinical Data

Diagnosis	Previous Allergy	Nature of Reaction	Anti-Pericious Anemia Liver Fractions Beef or Pork	Results and Disposition
1 L H Age 65 Pernicious anemia Asthma Urticaria	Asthma Urticaria	Asthma and urticaria Several repeated reactions in process of "desensitizing"	Positive scratch and intracutaneous reactions to all products as high as 1 100,000 First tests made 2/19/38	Tests still strongly positive 3½ years after first tests Only partial desensitization accomplished by repeated injections
2 A Q Age 52 Pernicious anemia	None	Generalized urticaria and vomiting Repeated mild reactions in process of "desensitization"	Positive scratch and intracutaneous reactions to most products First tests made 7/15/39	Desensitization continued intermittently for one year to August 24, 1940
3 M T Age 68 Pernicious anemia Hay fever	Hay fever for 20 years	Generalized itching and tightness in chest	Positive scratch and intracutaneous reactions to several products First tests made 6/15/40	Tests repeated 12/28/40 Still strongly positive
4 P P Age 43 Pernicious anemia	Urticaria 10 or 12 years ago	Urticaria	Positive scratch and intracutaneous reactions to several products First tests made 12/18/39	Tolerating injections of beef liver extract
5 W H Age 46 Pernicious anemia	None	Urticaria, nausea and weakness	Positive scratch and intracutaneous reactions to several products First tests made 12/14/40	After discontinuing injections for six weeks, he was able to continue them without reactions
6 F E Age 47 Pernicious anemia	None	Itching rash	Positive scratch and intracutaneous reactions Tests made 7/6/40	Continued with injections without reactions
7 M S Age 19 Acne Hay fever	Hay fever Perennial rhinitis	Urticaria and faintness on first two reactions Asthma on third	Positive scratch and intracutaneous reactions as high as 1 100,000 First test made 11/16/40	Tests made 7/15/41 show no reduction in sensitivity
8 J P Age 68 Pernicious anemia	None	Itching of skin Angioneurotic edema and dyspnea	Positive scratch reactions to several products	Injections discontinued

TABLE II
Immunological Data

A-1 Fraction	Anti-Pernicious Anemia Liver Fractions Derived from Other Species	Liver Protein Fractions and Liver Juice	Organ Extracts Prepared According to Anti-Pernicious Anemia Method	Muscle Protein Fractions (Beef and Pork)	Protein Fractions from Other Organs	Tapeworm and Ascaris	Other Reactions	Antibodies
1	Horse—positive Human—negative	Positive, but weaker than anti P A fractions	Kidney and stomach gave moderate reactions Muscle, negative	Negative	Kidney and stomach moderately positive Muscle, negative	Negative	Cattle hair, and hog hair, and house dust	Reagin—positive
2	Horse—negative Human—negative	Negative		Negative	Negative	Negative	Negative	Reagin—positive
3	Horse—positive	Negative		Negative			Ragweed	
4	Horse—positive	Negative	Negative	Negative		Negative		
5	Horse—positive	Slight reactions		Negative				Reagin-positive Precipitins—negative
6				Negative				
7	Horse—moderately positive	Moderate reactions		Negative	Negative	Negative	Grass and ragweed pollens House dust	Reagin—positive Precipitins—negative
8	Horse—moderately positive	Negative		Negative				

In four of these patients tests with liver extracts were made at various times and at the last testing they were found to be still strongly positive. This was the situation in Case 1 after three and one-half years, in Case 2 after 13 months, in Case 3 after six months and in Case 7 after eight months. The course of the skin reactivity of the remainder of the patients is not known.

DISCUSSION

According to our experiences, allergy to liver extract is not as uncommon as is indicated from the relatively few cases reported in the literature. During the three and one half year period from the beginning of 1938 to the middle of 1941, we have given parenteral liver therapy to 48 patients with pernicious anemia in the clinic and in private practice. Of this number, six patients (12.5 per cent) acquired sensitivity to the commercial liver extracts. In view of the large number of persons, with or without pernicious anemia, who are receiving liver injections, it would seem that allergy to these preparations is a fairly common phenomenon.

It is possible that the common usage of the long interval method allows more ready sensitization. This would be in conformity with experimental work on hypersensitiveness in animals, with many observations on other types of induced allergy in man and with the histories of the patients described in this paper. There is also the possibility that we may be dealing here with a special type of antigen which sensitizes rather readily. Although we do not know the exact chemical nature of the antigen, it can be stated that in some way it is associated with antianemic principle.

The degree and seriousness of the allergic reactions vary widely. In general, there can be observed a definite relationship between these factors and the subsequent management of the patient. Those with marked constitutional reactions and high degree of skin sensitivity are generally unable to tolerate liver injections, even after considerable intervals.

The question arises as to the course available when a distinct allergic systemic reaction has occurred. Several solutions of the difficulty are possible. As already noted, in some of the mild cases injections may be continued with no ill effects. In some instances this may be aided by a temporary discontinuance of the injections. In one case the difficulty seems to have been solved by a change to a liver extract derived from beef*. It is also possible that in the more difficult cases a course of desensitizing injections may produce a sufficiently high level of tolerance. It is quite definite, however, that in a number of instances of liver allergy therapeutic doses cannot be tolerated at any time. In such eventualities we must confine ourselves to the use of liver orally, which fortunately is usually well tolerated.

The observations recorded in this communication and some of the details omitted for the sake of simplicity open up a number of controversial im-

* Beginning a few months ago Lederle's Concentrated Liver Extract (1 cc = 15 U.S.P. units) is being prepared exclusively from beef liver.

munologic questions We feel that this is not the place to discuss all of these aspects but several of the more fundamental deserve comment There can be no question that in this group of allergic reactions we are dealing with a special antigen which is not the ordinary species specific antigen The organ tissues other than the liver did not contain such an antigen (with the exception of one special case) The pressed liver juice, rich in proteins, contained only a trace of this antigen The precipitated liver proteins contained practically none of this reacting substance It is quite apparent, then, that this antigen is neither the ordinary liver protein nor closely bound to it The antigen is not species specific, nor strictly organ specific, but it is specific as a special organ fraction, bound up with the antianemic fraction

A fraction of liver could be further isolated by precipitation of some of the commercial injectable liver preparation with acetone This precipitate, when subjected to chemical analysis by Professor Chester A Farmer,* showed no trace of protein discernible by the finest chemical tests and no evidence of the presence of carbohydrates, but it did contain 10 per cent of nitrogen, probably mostly in the form of amino acids It is of interest to note that this protein-free (chemically) substance was able to give specific intracutaneous reactions in dilutions as high as 1 1,000,000 Some of the commercial liver extracts also failed to show proteins by chemical tests This suggests another interesting point of departure in the concept of the nature of antigen and in the mechanism of allergy Immunologically specific immediate whealing reactions are elicited mainly by protein antigens In recent years some specific carbohydrate fractions have also been shown to possess this property Drugs and simple chemicals can cause typical and violent constitutional reactions of the atopic variety (asthma, hay fever, etc) but as a class they are known to be devoid of skin reacting properties In these liver fractions, however, we seem to have an antigen which is essentially free of protein, is capable of producing violent atopic manifestations, and readily produces immediate cutaneous reactions This would suggest the need for more extensive study of antigens from the point of view of other concepts than the orthodox protein theory

The criticism may be presented that our experiences do not necessarily demonstrate a special organ specificity, but that the process of extraction of the antianemic principle may constitute a better method of purifying or concentrating the usual species or organ antigen The following brief reports are an answer to such possible criticism

M H, a 19 year old girl, was seen with the complaint of asthma of four years duration Among other reactions there were definite cutaneous responses to the proteins of beef and pork (muscle) and horse serum The pressed juice of beef and pork muscle, as well as the juice of the livers of these animals, reacted intracutaneously in dilutions of about 1 100,000 Several of the brands of liver extract employed for pernicious anemia gave reactions from weakly positive to definitely negative An anti-pernicious anemia fraction obtained from horse liver gave a nega-

* Chairman of the Department of Chemistry

ve test It is clear, then, that here we are dealing with a totally different type of lergy, one having to do with species specificity, confined to no particular organ muscle, liver or serum), apparently residing in the protein fraction, and being snt or present only in traces in the antianemic liver fraction

Mrs N F, a 47 year old housewife, consulted us because of an allergic rhinitis id asthma of about 20 years' duration In addition to other more significant skin actions she showed positive cutaneous tests to beef and lamb The unpurified exact of beef liver gave strongly positive reactions whereas the pork liver failed to act The anti-pernicious anemia fractions gave questionable reactions As in the receding instance here we are apparently dealing with a species specificity rather an an organ fraction specificity

Further experiments suggest themselves for the more complete clarification of this type of allergy Liver fractions from widely divergent animal ources, such as chicken and fish should be tested The antigenic effect of he antianemic fraction in the laboratory animal deserves investigation The etermination of the exact chemical nature of this antigen in anti-pernicious nemia extracts may point the way to a better understanding of the characteristics of antigens in general And finally, the preparation of other fractions from animal and vegetable sources by methods employed in the preparation of this liver antigen may prove to be a generally useful method of solation of antigens Some of these suggested experiments are under way, but their discussion here is at present unwarranted

SUMMARY

Allergic reactions to injections of liver extract are reported in a series of eight cases, six of whom were receiving the material for pernicious anemia, one for anemia of undetermined nature and one for acne It is suggested that this type of induced allergy is not uncommon Cutaneous and intracutaneous tests with various fractions of liver and other organs of several species of animals indicate that this type of allergy has neither a species specificity, nor an organ specificity involving the usual protein antigen The specificity appears to be limited to a special fraction of an organ (liver) not bound with the ordinary protein fractions but associated with the antianemic fraction In addition to the practical importance of the occurrence and the management of this type of untoward result of liver therapy, attention is called to the potential immunologic significance of the demonstration of an antigen residing in a fraction of an organ tissue Attention is called further to the possible significance of the demonstration of a highly potent antigen containing no protein and yet exciting skin reactions

REFERENCES

- 1 HARTEN, M, and WALZER, M Allergy to insulin, liver, pituitary, pancreas, estrogens, enzymes, and similar substances, Jr Allergy, 1940, xii, 72
- 2 GRUEN, G Hypersensitiveness to parenterally administered liver preparation in a case of pernicious anemia, Wien klin Wchnschr, 1934, xlvii, 751

- 3 DIENA, D Hypersensitivity to liver preparation, *Gior d r Accad di med di Torino*, 1938, ci, 462
- 4 LASCH, F Concerning allergic symptoms due to parenteral liver therapy, *Wien med Wchnschr*, 1936, lxxxvi, 126
- 5 CRIEP, L H Allergy to liver extract, *Jr Am Med Assoc*, 1937, cx, 506
- 6 PASCHE, H D Observations on a case of allergy to liver extract, *Deutsch med Wchnschr*, 1939, lxxv, 1192
- 7 JONES, C A Allergic reactions following the parenteral administration of liver extract, *New Internat Clin*, 1939, iii, 259
- 8 GRAY, I, and BOWMAN, K. L In press
- 9 ENGEL, L Anaphylaxis to a liver preparation in a case of pernicious anemia, *Bol Assoc med de Puerto Rico*, 1933, xxv, 326

CARDIAC PROBLEMS IN WAR TIME *

By PAUL D WHITE, F A C P , *Boston, Massachusetts*

I SHALL not discuss the cardiac problems in war time which are also those in times of peace and which include the vast bulk of all the problems that both civilian and military doctors have to face, such as the diagnosis of coronary and rheumatic heart disease, the treatment of angina pectoris and myocardial failure, acute pericarditis, and arrhythmias. I shall plunge at once into the specific problems bearing on the heart in this year 1942.

First, a brief word about the cardiologist himself. His rôle is not a simple one. If a civilian, he is overburdened with the cardiac responsibilities of the folks at home, young and old, in caring for their acute and chronic illnesses and in helping to weed out from among the candidates for Navy and Army those whose hearts are unfit and to pass for military service those under suspicion, whose hearts are really fit. If a military man, he has left his hearts behind him. Theoretically, and practically too, most cardiologists who have donned the uniform have little of their specialty to perform, in the recognition and care of an infrequent cardiac patient who develops *de novo* or who has slipped through the examiners into service. Many of my cardiological friends in Army or Navy, though often busy, only in rare instances are busy with heart patients. They direct general medical services in camp or station hospitals or run infectious disease wards or even help the surgeons or the experts in other fields such as venereal disease. This is, as it should be, for awhile at least, a broadening influence for them and useful for Uncle Sam. On the other hand, those of us still in civilian clothes are working very hard trying to keep up with the acute and chronic problems of the cardiac patients at home. We are envious of our fellows who are likely to sleep well most nights and yet at the same time pleased that we can continue to practice what we have been trained to do, even though it is under pressure. However, it looks, hopefully now, as if in not too long a time there will be relief for both groups, at the end of the war. Perhaps some cardiologists will come back with new interests to other fields of labor, but the cardiovascular problems still beckon and presage the need of extensive tillage in the future.

The second problem which I would present largely concerns those of us who remain at home. Able but aging men, and women too for that matter, have been called back from leisurely retirement to the strenuous days of business, professional, or military duties. Some of them are working much harder than they had ever worked before when they were many years younger. And some of them have hearts and arteries that are not capable

* Presented before the Midwest Regional Meeting of the American College of Physicians, Chicago, November 21, 1942, and before the Annual Meeting of the New York Heart Association, Academy of Medicine, New York, January 21, 1943.

of this strain, crippled by newly acquired or aggravated angina pectoris or by dilatation and failure of a previously overburdened heart in the case of hypertension or valvular disease. This has happened to a number of my own patients, despite attempts to avert trouble. It is in many cases a true hazard of war but in other cases it is more or less preventable. Both for the sake of the community and the nation, and for the individuals themselves we must try as best we can to protect them against unnecessary overstrain—we can help plan their programs. Some of them, however, will succumb no matter what we do; they are the unsung heroes and martyrs of the war.

I shall now pose four questions which concern both those of us who examine the registrants for the Army and those of you who have to do with them after they have been admitted as soldiers. They concern pulse rate, blood pressure, murmurs, and that condition of ill health called neurocirculatory asthenia. They remain as problems inadequately answered, but the airing of the problems and the expression of our personal opinions are assuredly worthwhile. So far as I am concerned today I speak as an individual and in no way officially.

The *pulse rate* is still a stumbling block. What is the range of the normal, which may be acceptable for military service? There are a number of ideas about this. For example, at present Mobilization Regulations 1 to 9 state that a truly persistent heart rate of 100 or over should be considered a cause for rejection. Some examiners follow this recommendation quite literally. On the other hand, some believe that a heart rate of 120 at the time of examination even on repeated examination, is quite all right. Lewis states that "emotion raises the pulse very easily, a persistent rate of 120 or even 140 during a single and brief examination has little significance." He also refers to drugs occasionally used to raise the rate, cordite and thyroid. It may not be possible to reexamine some of these men at leisure or at least adequately, and so a good many have probably been rejected for an unimportant tachycardia. Much less has been said about bradycardia, as slow rates are much more readily acceptable. For example, U. S. A. MR 1 to 9 state that a pulse rate of 50 or under is acceptable provided it is proved to be the natural pulse rate of the individual, and yet heart rates around 40 per minute have been seriously questioned.

I would like to give my own experience with normal heart rates, first as to tachycardia. Some years ago I counted the pulse rate of six possible winners of the Ashland to Boston Marathon run at the starting line immediately before the race began and at the finish line immediately after they had completed the 25 mile distance. Their pulse rates before and after were respectively as follows: 64 before and 136 after, 86 and 120, 60 and 140, 62 and 108, 80 and 80, and last but not least 118 and 110. The last man whose pulse rate was the fastest by a considerable margin at the starting line was the easy and comfortable winner of the race in close to record time and his heart rate actually came down during that gruelling test. That experience taught me a lot, as did the observation of a fall in heart rate of a

nervous but husky Marine candidate in my own quiet office in the course of an hour from 130 to 65 per minute, proved by electrocardiogram.

Recently I have had the opposite or slow heart rate range brought to my attention. Some of you may have noticed a letter on the extreme bradycardia of distance runners in the *Journal of the American Medical Association* of a few weeks ago. Three perfectly normal champions of long distance running, a miler, a two miler and a Marathoner, and an aviator had proved basal heart rates of 37, 38, 35, and 38 per minute respectively. Doubtless there are more that I haven't heard about, and pulse rates in the forties are common among athletes. Only the other day a professional man aged 62 came into my office for a check-up after an excellent recovery from a myocardial infarction. His heart rate was 43. I thought that perhaps this slow rate might have resulted from the coronary heart disease, but I also thought to ask him if by chance he had ever done any distance running in his youth and he answered "yes," that he had been captain of the Yale cross country team over 40 years before and had always had a slow pulse.

Thus my own conviction from simple clinical observation during the last 25 years is that the normal pulse rate, at rest or relative rest, even in outstanding athletes, has a tremendous range, actually from 35 to 118 per minute.

Next, the question as to *blood pressure* is harder. Opinions differ as to the upper range, particularly of the systolic level in a young man. MR 1 to 9, although setting a limit, allows freedom of interpretation and judgment about that limit; thus a cause for rejection is a "persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, *unless* in the opinion of the medical examiner the increased blood pressure is due to psychic reaction and not secondary to renal or other systemic disease." This question of the blood pressure remains for the day our most difficult cardiovascular problem, strictly as such, neurocirculatory asthenia only secondarily being a problem, though a hard one, for the cardiologist.

How high may the blood pressure normally rise on excitement, at physical rest, and not represent a threat for the future? No one has adequately answered that question as yet. One can certainly be more liberal with the systolic level. Lewis, for example, has been very much so. He wrote in 1940 that "single readings of systolic blood pressure up to 180 mm. Hg in soldiers who are out of bed are not of much value in diagnosing essential hypertension," that "readings of 230 and over are much more significant," that "readings as high as 180 are not infrequent in 'effort syndrome' cases, effort or excitement carrying readings to high points in these," and that "essential hypertension should not be diagnosed unless successive readings such as 180 to 200 have been recorded in the subject lying at ease and completely rested; preferably it should not be made until such readings have been taken with the subject in bed." But undoubtedly we should be much more concerned with the diastolic level.

Among the hyperreactors to excitement, to effort, to cold, and to drugs are

probably most of the hypertensives of the future. We must go beyond Lewis' attempt to diagnose clear cut essential hypertension at the time of the examination and try to weed out the cases which sooner or later will develop the condition, in 5, 10, 15, or 20 years and in a few rapidly developing cases even in a year or two, unless the pressure for manpower is excessive, and it has not yet reached that point. Why should we try to be so careful? In the first place because some of these hyperreactors come to grief rapidly, secondly because the strain of military service may in some cases accelerate or precipitate the process, and, last though perhaps not least, as the Veterans' Bureau constantly is reminding us, we taxpayers will be penalized in years to come to pay for the disability of men whose hypertension may have developed in service or can in any way be service connected. However, in the present state of governmental development here or elsewhere this last argument may not for the moment be so much a medical as a political problem, unless a radical change takes place from the medicopolitical status of the veterans after the first World War. Despite this gloomy foreboding concerning the probability of decision as to service connection of the dim and distant hypertension in veterans of the present war, we can and should do something about the problem, and not shut our eyes to it as too difficult. We can at least make studies which will be helpful for the future, even for future wars or at least for the future employment of the international military forces that will be needed to police the world for a generation or more to come.

It would, of course, be convenient to shut our eyes to the problem by omitting the taking of blood pressures altogether in the registrants inasmuch as not many true established hypertensives among these young men would thereby be admitted to service. We need this very information, however, in projected studies which cannot be supplied by statistics from insurance or college or other groups despite the valuable hints from those sources. One study about to begin which we hope will bear fruit is to review the annual blood pressure and health records of our own military officers dating back to the days of the earliest routine blood pressure measurements. We hope that we may secure useful information about the future of men who start off with so-called high normal pressures in contrast to that of those who begin with low normal pressures.

Not only are we concerned with the health record of the men we admit to the Army and Navy but we are concerned with their efficiency record too. The efficiency of an army is more important in the final analysis than our ideas about its health, though of course, as a rule the two apparently go hand in hand. However, it has been suggested that men with high normal or even slightly elevated blood pressures are stronger and more alert and have more endurance, on the average, than those with low normal or slightly depressed blood pressures, say 150 to 160 systolic and 90 to 95 diastolic in comparison to 100 systolic and 65 diastolic. This may be so and perhaps the related question that has been asked is appropriate, namely "Do we want a long-lived

army or an efficient one?" But it is not so simple as all that, nor do we have the facts as yet.

Figures already gathered do indicate that among the youthful hyper-reactors will be the hypertensives of tomorrow, but we don't know what percentage or which ones. One college follow-up showed only a minority still in the higher range ten or more years later, and we lack adequate military follow-up. Hence the proposed study.

Meanwhile what is the sensible thing to do about the blood pressure? I expect it is to follow the middle of the road. During 1940 and 1941 too many registrants were doubtless turned down all over the country for so-called hypertension. The interpretation of the figures was too literal and brusque, and I expect that we can salvage quite a few of those rejectees. Recently, on the other hand, with the letting down of the bars all around, it is probable that hypertensives, present and future, are slipping in too freely. I understand that we are not in such dire need of manpower as to admit these men as yet. We can still be choosy, especially with the older registrants, from 36 to 45, who constitute the greatest hazard and who illustrate perhaps what the status of the veterans now 20 to 30 years old will be in 1957. I was told recently that whereas 7 out of 10 registrants aged 20 to 28 are passed as physically fit, only 3 out of 20 of those aged 36 to 45 are so qualified. This important fact speaks for itself.

Shall we continue to use the figures for blood pressure in MR 1 to 9 of acceptable upper levels of 150 mm. systolic and 90 diastolic at rest or shall we raise them? It is my personal opinion that if we do raise them at all it shouldn't be by much. Perhaps under the excitement of the examination 160 might be acceptable as the upper limit of the systolic pressure, but I wouldn't raise the diastolic level much if any. I am dubious about even a 5 millimeter raise, that is, to 95. For the time being, with these remarks about the rules and our ignorance in general and in particular, the common sense of the examiners must be largely relied upon and that's about all I can tell you of my thoughts concerning this important subject of the range of normal blood pressure.*

The next problem that I shall speak of is that of *heart murmurs* among the candidates for Army and Navy. In 1940 and 1941 too many perfectly fit young men were being turned down because of the finding of inconsequential physiological murmurs, whereas relatively few cases of actual heart disease were slipping through when the finding of certain murmurs should have held them up. In recent months, however, the tide has turned, with the letting down of the bars, and men with real cardiac diseases are unfortunately being admitted in too large a number. Shortly after the A.E.F. reached northern Ireland, a medical friend of mine in one of the larger hospitals there wrote me about the dull but encouraging dearth of any cases of cardiovascular disease arriving in his wards; it was a rare and exciting

* It is quite probable that increase in blood pressure due to nervousness associated with increase in pulse rate is less important than increase in blood pressure with a slow pulse rate.

occasion when a congenital or rheumatic heart lesion came to light, usually mild and not too readily diagnosed. But only the other day when I visited a camp hospital the medical officers had lined up for me to see a group of men with very obvious valvular heart disease, who should never have been admitted at all, but who were passed recently, either because the examiner was deaf or tired or nonchalant about them. One of them was passed intentionally because his murmur was only a systolic one, a hangover from the casual disregard of murmurs that held for awhile during and shortly after the last World War, in part because of Mackenzie's needed reassurance about murmurs during the pressing demand for manpower for the British Army. That man's murmur, however, was a loud one at the apex, the heart was definitely though not greatly enlarged, and there was a perfectly clear history of rheumatic fever. It was really ridiculous to enroll him, simply on the basis of the timing of the murmur. Of course he was not in failure and his functional state was good, but there are two important reasons, nevertheless, why such cases should all be rejected, for combat service at least. In the first place, there is present structural heart disease involving heart valves and heart muscle which under the strain of war can develop arrhythmia, dilatation and failure, or even subacute bacterial endocarditis, no matter how fit the person seems to be at the moment. And secondly, there is the very definite hazard of recurrent rheumatic fever in these cases after exposure to infection with the hemolytic streptococcus, a far greater hazard than in those who have not previously had rheumatic fever or if they have had it, at least have not had permanent valvular deformity or cardiac enlargement resulting. Rheumatic fever, even in epidemics, can develop in the Army and Navy, but it will not be much of a problem if we weed out these obvious rheumatic cases at the source. I believe also, by the way, that if acute rheumatic fever does develop in service in a man without previous heart damage and is brief and leaves no residual effect on the heart it need not in every case necessarily be a cause for discharge from service.

What murmurs, then, are acceptable and what are rejectable? Let us take the latter first. All diastolic murmurs are abnormal and so are all loud or moderate persistent systolic murmurs at the cardiac apex, aortic valve area, and at the left of the lower sternal border. So too are very loud or even loud pulmonary valve systolic murmurs if persistent in all body positions and phases of respiration. Acceptable, that is, physiological murmurs are in the main pulmonary in location and systolic in time. They vary with both body position and respiratory phase, being loudest in the supine position and in full expiration, and becoming faint or disappearing in the upright position or at full inspiration. Other murmurs that may be passed as normal are those produced in the lungs by the heart beat itself, that is, the sound of currents of air and not of blood, and secondly, trivial or at most slight systolic murmurs at apex, aortic area, or over the lower sternum which tend to disappear like the louder pulmonary systolic murmurs with changing body position or respiratory phase. But it is important to remember that, at least in adults

who are not ill with anemia or acute infections, apical and aortic systolic murmurs are usually indicative of pathological conditions in heart or aorta.

Finally, I would say a few words about *neurocirculatory asthenia* even though it has been moved in the Army and Selective Service listings from under the cardiovascular heading to that of neuropsychiatry where it may not really belong either. It can be made to fit everywhere for it is evidently a condition that can follow or attend all sorts of diseases. It is, I believe, best defined as I gave it in a recent leaflet of the American Heart Association, one of their so-called Modern Concepts of Cardiovascular Disease (the August number): "Neurocirculatory asthenia is a condition of ill health characterized by a group of symptoms consisting of dyspnea (often with sighing respiration also), palpitation, precordial pain (more often an ache), exhaustion, dizziness, nervousness, and sometimes tremor, sweating, headache, and syncope, aggravated by effort or excitement, and attending or following infection or physical or nervous strain, especially in 'hypersensitive' individuals, who in extreme cases may show the condition more or less constantly with little or no provocation." In other words it is not a specific disease itself as far as we know, although it may in some cases seem to stand more or less alone. Its pathogenesis is unknown. As good a suggestion as any is that it is a disorder of the vegetative nervous system precipitated by a variety of factors which in peace time or in training camps in war time are predominantly the anxiety psychoneurosis and infectious disease, but which in the stress and strain of combat can include physical and nervous exhaustion, then being rather a fatigue syndrome. Naturally, therefore, both in peace and in war the psychoneurotic looms largest among the subjects with the condition and the syndrome has therefore sometimes been labelled as "anxiety neurosis." I believe, however, that it is best to consider it rather as a result or accompaniment of an anxiety neurosis, since I have seen patients neurotically anxious about their hearts without these characteristic symptoms and I have seen other patients with these symptoms who had never been nor were at the time, so far as I could tell, afflicted with any psychoneurosis. Yet despite its varied etiological background neurocirculatory asthenia is a condition of ill health that exists and as yet in my opinion cannot be designated by any better term. Undoubtedly it has been labeled as but a part of its exciting factor in the majority of cases when it is relatively mild and its exciting factor prominent, as in the case of some acute infectious disease, fatigue state, or psychoneurosis. But sometimes the exciting factor is not so evident or the syndrome itself is of considerable degree, and then it stands as the main diagnosis. Hence it has not loomed large among the causes for rejection from the armed services even though it is a common and sometimes marked finding in many of the cases turned down, and rightly so, for a psychoneurosis.

Among the men whom Drs. Cobb, Graybiel, Cohen, Chapman, and I have already seen and studied in army hospitals with the label neurocirculatory asthenia, a psychoneurotic state, chiefly an anxiety neurosis, stands pre-

eminent and was present in almost every case, and nearly always was quite marked before enlistment. These men are obviously constitutionally inferior and should never have been admitted to the Army. I really doubt whether we are justified in passing any at all who have the condition under the lesser strains of peace time despite the recommendation in MR 1 to 9 that we may accept registrants with neurocirculatory asthenia if it is very mild in degree. We did recently add the "very," but it is more and more my belief that if the condition can be recognized at all in peace time and is not provoked by some correctible factor, the registrant should be rejected, for these cases become awful headaches for the doctors in service. One should not admit them with the idea that training will help them to outgrow their state of ill health.

It's another matter when neurocirculatory asthenia appears for the first time after enlistment. The more severe the strain needed to bring out the condition, the less need be our concern about it. Rest for a few days or a few weeks should relieve the symptoms and an attempt should be made to avoid soon subjecting that person again to such a severe strain. But when preliminary or only moderate drilling induces neurocirculatory asthenia and a careful training program does not quickly alleviate it, either the soldier should be discharged if his limitations are great or given less strenuous or more suitable tasks (if possible) if his limitations are only slight to moderate. We should be able to exclude enough of these men at the source so that we shall not be in the predicament that faced the British after the last war when they were saddled with 44,000 cases of "effort syndrome" who became pensioners, or that faced DaCosta who wrote as follows: "The treatment is never a short one; and the question arises, would it not be better for the government at once to discharge these heart cases? I think not. The very worst ones, those which after some months of treatment show no decided improvement, had better be discharged; so had those which happen in the very young, or in soldiers in whom some decided complicating ailment exists, which is likely to prevent the cardiac malady from entirely leaving; though even some of these can be kept as fit for guard duty, for service in hospitals, or in convalescent camps. But all other cases should be kept for treatment; and then either, if fit, sent back to their regiments, or passed into such organizations as the Veteran Reserve battalions during the late war,* which were intended to do provost duty, to serve in fortified places, in fact, to do everything except active service in the field. And from these organizations again, should the war prove a protracted one, the cases that have thoroughly recovered may be sent to rejoin their former regiments. To act otherwise, to discharge the large number of cases of functional disorder of the heart, which must exist in every army during war, would, I believe, deplete it as much as an engagement, and have on many a soldier, seeing the ease with which a discharge can be obtained, a demoralizing effect. As for the time required before the disposition of a case is made, this depends much on judgment in individual

* Our Civil War.

instances, and while, until I understood the malady, I retained a number of patients a long period in the hospital, later in the war a short time sufficed to make a proper disposition of them."

To avoid DaCosta's dilemma and that which faced the British Army, and ourselves too for that matter, during the first World War, we must attempt to weed out of the registrants those individuals who are obviously afflicted with the condition in peacetime. Even if we are able to do that we shall still have enough cases among the soldiers of tougher fiber when the fighting gets rough enough, but we should expect to avoid the great majority of the military neurocirculatory asthenic cripples of former days. Since in peacetime the characteristic neurocirculatory asthenia patient is a psychoneurotic with an anxiety neurosis, it is to the psychiatric part of the induction examination that we should naturally turn for help. I believe that such examination has already borne rich fruit for we find that relatively few very definite cases of neurocirculatory asthenia actually have been hospitalized through the U. S. A. as yet. Let us hope that this may be the answer, and, if it is, stress still more the importance of the psychiatrist with his feet on the ground, in any examining group.

Exercise tests such as Lewis suggests may be useful too, but they are open to a number of objections: first, the difficulty of giving each man an appropriate exercise for his degree of physical training; second, the uncertainty of the results on occasion, as, for instance when the registrant has caroused the night before celebrating his departure for the Army or for other reason; and third, though less important, because of the extra trouble that such a test entails. Certainly, when one is in doubt, however, recourse should be had to some simple exercise such as stair climbing, or the chair mounting or two-step test.

My time is up, but I hope that I may have helped to clarify in your minds our chief cardiac problems in war time in this year 1942 even if I have been unable to give you all the answers.

MYXEDEMA HEART: A PATHOLOGICAL AND THERAPEUTIC STUDY *

By JOHN S. LA DUE, M.D., *New Orleans, Louisiana*

THIS report presents the autopsy findings in a patient dying of heart failure due to myxedema and points out the similarity of her myocardial lesions to those found in the beriberi heart. The case history of another patient with myxedema heart treated with thiamin and vitamin B complex and then with thyroid extract is reviewed.

The clinical syndrome of heart failure sometimes associated with hypothyroidism (myxedema heart) was first described by Zondek¹ in 1918. It was later recognized in this country by Fahr² and has since been discussed by many investigators.³ Hallock⁴ showed that the cardiac output of the myxedema heart was low and that it was increased by the administration of thyroid extract. Descriptions of the pathological changes in the heart muscle are few and controversial.

Schultz⁵ described the pathological findings in a 12 year old girl with congenital athyrosis who died from myxedema heart failure. The heart was generally dilated, the muscle pale, and a normal amount of pericardial fluid was present. The cardiac muscle cells were filled with hydropic vacuoles and there were fragmentation and branching of individual fibers with loss of striations. These vacuoles did not stain for fat or mucus. Mucus was found in the wall of the aorta and in the perineurium of some of the nerves.

Behr and Milder⁶ published an autopsy report of a patient with myxedema heart with severe congestive failure who died after five days of intensive thyroid therapy. The heart was generally dilated, weighing 335 grams, the muscle pale with rather extensive fibrosis and narrowing of the coronary arteries. Histologically, besides the fibrosis, the muscle cells stained irregularly. Many fibers were swollen, their nuclei pyknotic and the striations absent. In many cells the sarcoplasm was replaced by hydropic vacuoles. These changes were most pronounced in sections taken from the subendocardium, although they were found diffusely. The vacuoles failed to stain for fat, mucus or glycogen. Webster and Cooke⁷ noted similar involvement in the myocardium of rabbits 185 days after complete removal of thyroid tissue. Brooks and Larkin⁸ were unable to detect such changes 40 days after thyroidectomy.

Elsewhere in the literature⁹ reports are inconclusive because autopsies were performed long after thyroid therapy was begun or because microscopic studies were not made and unusual myocardial involvement was hence not noted.

* Received for publication April 22, 1941.

From the Department of Medicine at the Minneapolis General Hospital and the University of Minnesota Medical School, Minneapolis, Minnesota.

Lufkin¹⁰ has briefly reported the pathological findings in a woman dying of hypothyroidism associated with severe heart failure. A more complete review of the clinical and pathological picture exhibited by this patient is herewith presented with his consent.

CASE REPORT

The patient, a 52 year old housewife who entered the Minneapolis General Hospital on November 29, 1936, had had intermittent dyspnea, orthopnea and edema of the lower extremities for two years, with increasing distress since June, 1936. An informant stated that since 1929 the patient manifested increasing weakness and fatigue and had come to do her household work with maddening slowness. Relatives

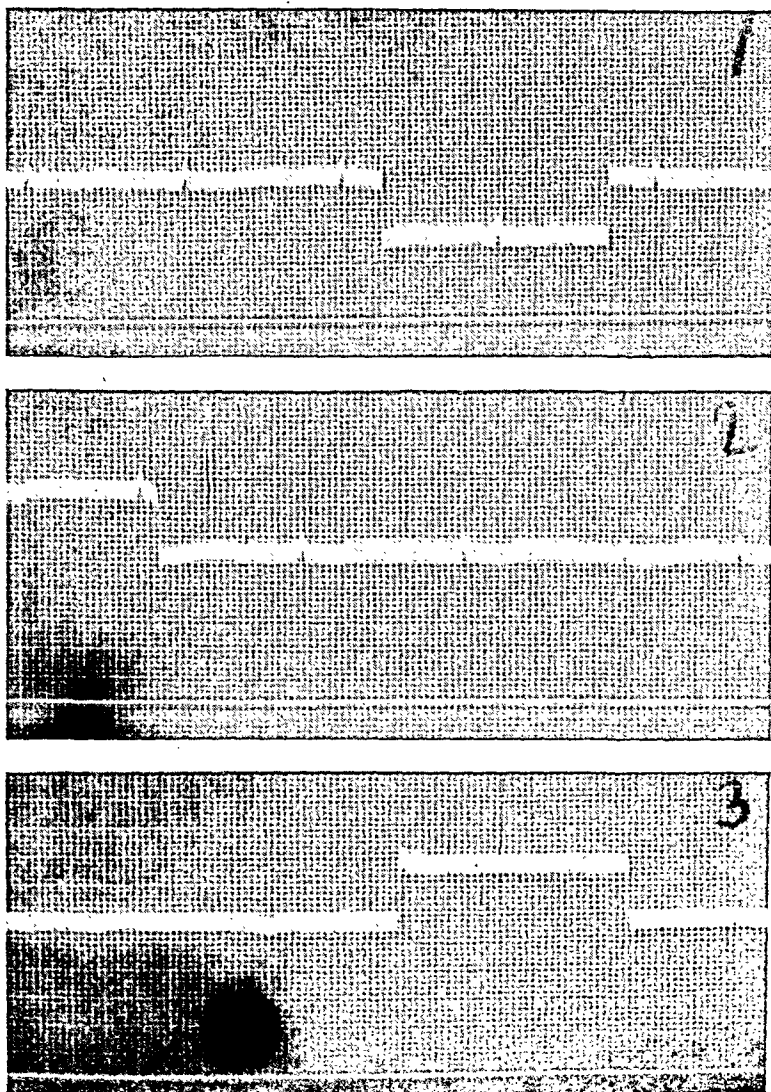


FIG. 1. Electrocardiogram taken six hours before death showing an extremely low potential, at its highest only 0.2 millivolts. T_1 is isoelectric, T_2 and T_3 are negative. These changes are consistent with myxedema heart.

said that a marked slowing of her mental processes, together with extensive loss of memory, dated from 1933. About a year later other changes were noted. She complained bitterly of chilliness, her voice grew increasingly hoarse, and despite loss of appetite she gained weight. Weakness progressed markedly, her complexion became pale and she sat about apathetically, refusing to move unless it was absolutely necessary. Various physicians treated her for heart failure, kidney trouble and anemia. Liver extract and digitalis were taken without improvement. Physical examination revealed a moderately obese patient who was unable to answer questions. She was markedly cyanotic, propped up in bed and gasping for breath. Her hair was coarse and her eyebrows scanty; the face and eyelids were swollen and the lid slits narrowed. The skin was dry, thick and pale yellow in color. The neck veins were distended, but the thyroid was not palpable. There was dullness over both lung bases and crepitant râles were heard. The heart seemed enlarged to percussion, the rhythm was regular, the tones were faint, and no murmurs were heard. The blood pressure was 115 mm. Hg systolic and 70 mm. diastolic. The abdomen was obese, with shifting dullness in both flanks, and the liver was felt 10 cm. below the costal margin in the right midclavicular line. There was massive pitting edema of both lower extremities. The clinical diagnosis was hypothyroidism with myxedema heart in congestive failure.

The hemoglobin was 47 per cent, the specific gravity of the urine 1.018 with a faint trace of albumin and 6 to 8 white blood cells per high power field. The electrocardiogram (see figure 1) showed an extremely low potential, at its highest only 0.2 millivolts. T_1 was isoelectric, T_2 and T_3 were negative.

The patient lived just seven hours, apparently dying of congestive heart failure. Autopsy was performed nine hours after death.

The body was that of a well developed, obese woman weighing approximately 200 pounds. Rigor and hypostasis were present. There was massive edema of the legs, thighs and back, less marked over the dorsal surface of the hands and over the eyelids. The hair was thin, coarse and dry and the skin slightly yellowed.

About 1000 c.c. of straw colored fluid filled the peritoneal cavity; approximately 800 c.c. of amber fluid were found in the right pleural cavity and 400 c.c. in the left. The pericardial sac contained 30 c.c. of clear, watery fluid.

The heart was globular, weighed 400 grams, and measured 14.5 cm. at its greatest transverse diameter (figure 2). Both auricles and ventricles were dilated and their myocardial surfaces smooth and glistening. The valves showed no pathological changes. The left ventricle was moderately hypertrophied and dilated, the right slightly thicker than normal but greatly dilated. The heart muscle was pale red throughout and possibly a little soft, but no fibrosis or other focal lesions could be found when the muscle was sectioned. The coronary orifices were patent and of normal dimensions. The descending branch of the left coronary artery showed slight diffuse thickening without appreciable lumen alteration and two centimeters from its point of origin it divided into right and left rami. Here there was an atheromatous nodule which abruptly reduced the caliber of the left vessel to one-half. This nodule also extended 0.5 cm. into the right ramus, reducing its lumen to one-third. The other coronary vessels were free of significant changes.

The right lung weighed 450 grams, the left 500 grams. Crepitation was diminished throughout both lungs and a frothy fluid oozed from their cut surfaces.

The liver weighed 1300 grams and its lower margin extended 10 cm. below the costal margin in the right midclavicular line. The cut surfaces were slightly yellow, but scattered throughout there was evidence of chronic passive congestion with enlargement and reddish discoloration of the centers of the liver lobules. The gall-bladder contained two green calculi and its wall was somewhat thickened.

The stomach was filled with 300 to 400 c.c. of dark hemorrhagic fluid and blood clots. Near the antrum several ulcers, some superficial and others extending into the

submucosa, were noted. A few of these ulcers were surrounded by elevated margins; none was more than 3 to 4 mm. in diameter. The jejunum and ileum were filled with hemorrhagic material but the mucosa of the entire intestine was intact.

The pancreas, adrenals, genitourinary tract, uterus, tubes and ovaries appeared normal.

The dorsal aorta contained numerous small, soft, yellowish plaques.

The thyroid weighed only seven grams, was fibrous and contained no visible colloid.

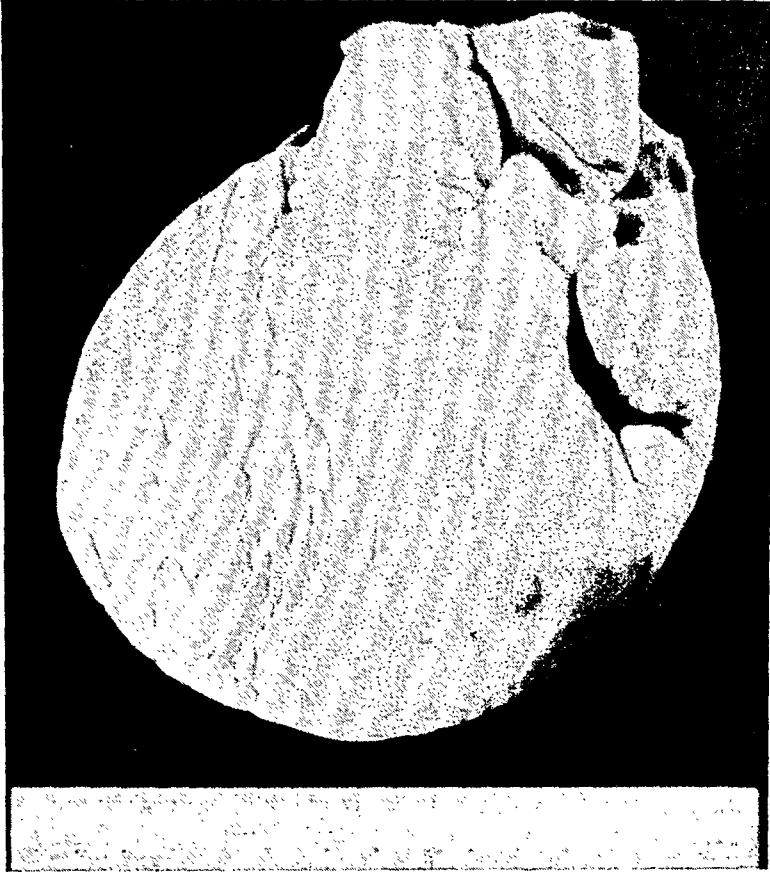


FIG. 2. Globular shaped heart of the patient dying with myxedema heart. Its transverse diameter is 14.5 cm. and it is generally dilated.

Microscopic examination revealed that the thyroid gland was markedly atrophied; many acini were replaced by fibrous tissue and only a few acini contained colloid. There were small areas of polymorphonuclear infiltration about the bronchi of the lungs and many alveoli were filled with red blood cells; heart failure cells were prominent. The centers of the liver lobules were packed with blood and surrounded by atrophied liver cells. Sections of the gastric ulcers showed loss of mucosa with edema and leukocytic infiltration about their edges and to a lesser extent in their bases.

Sections of the heart muscle just beneath the endocardium showed striking changes. In many places the sarcoplasm of the myofibrils was completely replaced by hydropic vacuoles. Elsewhere there were branching and loss of striation of individual fibers. Some of the cells were pale, others were deeply stained, small, and had

pyknotic nuclei. Stains of the vacuoles were negative for fat, mucus and glycogen, indicating a true hydroscopic swelling similar to that noted in the edematous tissues of patients with myxedema. These changes were present but much less pronounced in other sections of the myocardium.

These findings are the same as those described by Schultz,⁵ Behr and Müllder⁶ and Webster and Cooke⁷ and were thought to be specific by these investigators. Ceelen¹¹ has suggested that they are the result of changes (sclerosis) in the coronary vessels accentuated by the disturbance of lipid metabolism. Higgins⁹ also subscribes to this point of view, but states that early involvement of the heart may consist of "mucin-like infiltration of the muscle fibers which can be overcome by the judicious use of thyroid extract." However, the studies of Schultz,⁵ Behr and Müllder⁶ and of the case reported here indicate that the "mucin-like infiltration" is not mucus, fat or glycogen but hydroscopic edema. Arteriosclerotic damage of the myocardium was conspicuously lacking in Schultz's case, in the case described here and in many of the experimental studies. It is, therefore, probable that fibrosis of the heart muscle is not a specific result of myxedema.

In searching for evidence to prove or disprove the specificity in myxedema of such changes in the heart muscle as vacuolization, loss of striation, branching, inequality of staining and the pyknotic nuclei of muscle fibers, we tried to detect these processes in other types of myocardial disease. Dr. Lufkin¹² examined a series of hearts in elderly patients dying of heart failure and from other causes and discovered strikingly similar changes in the His bundles. In examining a series of dog hearts for other changes, I found many areas of involvement not unlike those seen in our myxedema heart. These animals had been unable to retain their feedings for as long as 21 days.

Wenckebach¹³ has stated that hydropic swelling of the myofibrils, loss of striation and intercellular edema are characteristic, if not specific, for beriberi heart. Weiss and Wilkins¹⁴ also detected these changes in 21 patients with polyneuritis and pellagra with or without cardiovascular dysfunctions. The myocardial fibers and conductive tissue of this group showed various degrees of hydropic swelling. Similar changes were seen to a lesser degree in a few of the hearts of 36 controls. These investigators concluded that these histological alterations were not indicative or specific in beriberi heart or in the hearts of patients suffering from polyneuritis and pellagra. Figure 3 illustrates the similarity of the histological changes in myxedema heart (photomicrograph from sections of the heart of the patient reported here) and beriberi heart (reproduced from Weiss and Wilkins). Both exhibit hydropic vacuolization of muscle fibers, branching and loss of striation.

Some time after the first report of this case, another patient with myxedema and myxedema heart in mild failure was admitted to the Minneapolis General Hospital and it seemed worthwhile to test the therapeutic properties of thiamin and the vitamin B complex on this patient. After a brief control period during which necessary laboratory studies were made, the patient was

given intensive vitamin B therapy for 33 days and the laboratory studies were then repeated. Thyroid extract was then administered and the laboratory studies again repeated. Findings are given in the case report.

CASE REPORT

The patient, a 43 year old housewife, entered the hospital on the dermatology service on December 7, 1939, asking to be treated for small yellowish nodules which had

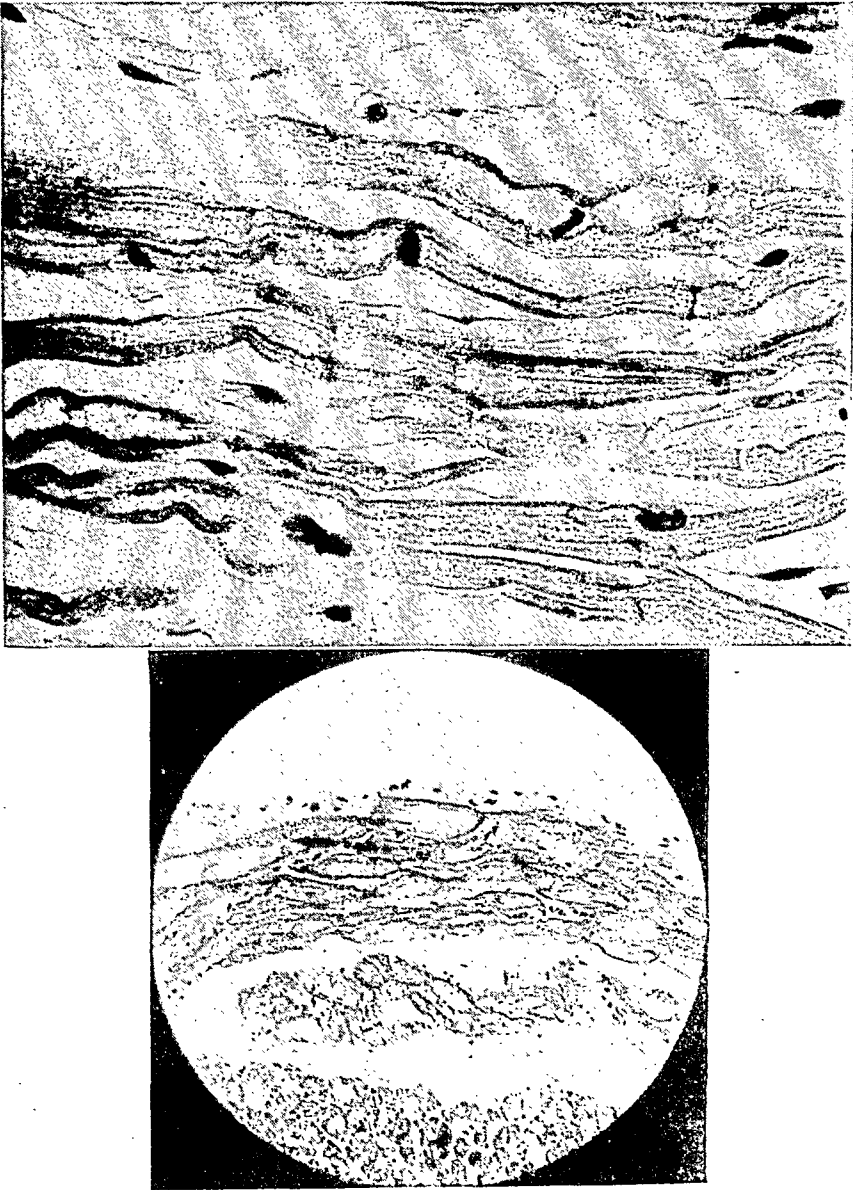


FIG. 3. (Above) Photomicrograph of myocardium of the heart shown in figure 2. Note replacement of sarcoplasm of the myofibrils by vacuolization. There is loss of striation and branching of some of the individual muscle fibers.

(Below) Photomicrograph from Weiss and Wilkins¹⁴ of a section of the myocardium of a beriberi heart. Note similarity to above.

appeared on her hands, feet and body during the preceding 18 months. She had also noticed increasing weakness, malaise, dry skin, hoarseness, cold sensitivity and impairment of hearing. The first change in her skin had been the appearance of a yellowish discoloration on the palms of both hands. Within six months small, painless, lemon-colored lumps had formed at the bases of the fingers; soon they were noted on the feet and later on the trunk. Her complexion grew muddy and yellow, her skin dry, coarsened and later wrinkled. Her hair had always been coarse and dry and her eyebrows scant but these faults were accentuated after the onset of the present illness.

Although these objective changes occupied most of her attention, she stated that she felt that she was becoming "old." She had difficulty in recalling recent events; conversation required great attention and quickly tired her. She was unable to concentrate or to formulate ideas and said that her speech was impaired because of a "thick tongue." Her voice became coarse and words had to be formed slowly. Her hearing, which had been excellent, became poor. One of the most distressing symptoms was the acute discomfort produced by moderate exposure to cold. Weakness was progressive, so that she was finally unable to do her housework, and she found herself irritable and short with her children. The menstrual cycle, previously normal, was irregular and the flow excessive.

A week before coming to the hospital she had noticed increasing swelling of the ankles, mild dyspnea on exertion and palpitation. There was no precordial pain.

TABLE I
Summary of Laboratory Data for Patient 2

Determinations	Control Period (Dec. 7-Dec. 21)	After Thiamin (Dec. 21-Jan. 23)	After Thyroid (Jan. 23-Feb. 26)
Basal metabolic rate	-28% and -24%	-35% and -37%	-8% and plus 10%
Roentgenogram Ml. Heart Mr.	9.0 cm. 5.9 cm.	8.8 cm. 5.8 cm.	6.8 cm. 4.8 cm.
Electrocardiogram	Typical for myx- edema heart	Unchanged	Normal
Cholesterol	540 mg. %	870 mg. %	268.4 mg. %
Hemoglobin	50%	55%	62%
Red cell count	2,530,000	2,920,000	3,270,000

The patient was a well-nourished, but not obese woman, who looked older than her 43 years. Her voice was hoarse and she spoke in a slow, drawling manner, pausing for several moments before answering questions. She did not seem dull, but reacted very slowly.

The face was wrinkled but expressionless, the complexion muddy yellow. The hair was coarse and brittle but fairly abundant; the eyebrows looked moth-eaten. The lids of the eyes were slightly edematous and a yellow nodule 1 to 2 mm. in diameter was seen on the right upper eyelid. The conjunctivae were pale and in the right there were four fatty nodules. The patient was edentulous and the mucosa of the mouth had a yellowish cast. The skin was dry and flaky. Both palms were a pale yellow color which was intensified in the skin creases. Yellow nodules 1 to 4 mm. in diameter were scattered diffusely over both palms and about the joints of the fingers on the backs of the hands. The nodules were freely movable and not tender. Similar lesions, 1 to 6 mm. in size were present on both knees, on the skin covering the Achilles' tendon, and on the dorsal and plantar surfaces of the feet.

The lungs were resonant throughout and no râles were heard. The heart was enlarged to percussion, ml. being 9.0 cm. and mr. 6 cm. The heart sounds were distant and faint, the rhythm regular, and the rate 86. No murmurs were heard, the aortic second sound was equal to the pulmonic second, and the blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The abdomen was soft and there were no



FIG. 4. Teleoroentgenogram and electrocardiogram of Patient 2, illustrating generally dilated heart and electrocardiogram typical of the myxedema heart, before any treatment was instituted.

palpable masses or viscera. The extremities were symmetrical, with a 2 to 3 pitting edema of both ankles. Reflexes were sluggish but equal. Both the knee and the ankle jerks had a normally active contraction but relaxation was unusually slow.

Most of the important laboratory findings are summarized in table 1. The serum proteins were within normal limits, with a globulin of 1.7 per cent, an albumin of 5.5 per cent and a fibrinogen of .16 per cent. On December 22, 1939, the vitamin C level

was 0.2 mg. per cent and before discharge it had risen to 0.8 mg. per cent. The phenol-sulphonphthalein elimination was essentially normal. A cholesterol tolerance test on December 21 gave the following: Fasting level 565, 2 hours 800 mg. per cent, 4 hours 571 mg. per cent, 8 hours 835 mg. per cent, 24 hours 835 mg. per cent. A glucose tolerance test on December 12 showed a fasting level of 85 mg., a peak of 155 mg. at one hour and a level of 120 mg. at the end of three hours. A biopsy of the skin from the right foot showed a diffuse edema of the subepithelial connective tissue. Numerous lipid-containing cells were scattered throughout the section and an edema and a cellular exudate were seen about the sweat glands. A microscopic section of one of the nodules showed fibrosis with cholesterol clefts within the fibrous areas. The basal metabolic rates, electrocardiograms and roentgenograms are included in the discussion of the course of the disease and summarized in table 1. Course: The patient was not seen by the medical service until the seventh hospital day. At this time there was no edema and the venous pressure was 8 cm. of sodium citrate (normal). No trace of congestive failure could be found. On December 8 the basal metabolic rate was —28 per cent and on December 14 it was —24 per cent. On December 16 a six-foot roentgenogram of the heart was made and these measurements reported: transverse thoracic 23.7 cm.; ml. 9.0 cm.; mr. 5.9 cm.; total 14.9 cm. and the arch 3.2 cm. Fluoroscopically, the pulsations of the heart were of decreased amplitude. There was no evidence of pulmonary congestion. An electrocardiogram taken the same day showed a low potential in all leads, isoelectric T_1 , extremely low T_2 , T_3 and an M shaped QRS₃ (figure 4).

In view of the clinical and laboratory findings, diagnoses of myxedema with myxedema heart and generalized xanthomatosis were made. No medications, except ferrous sulfate gr. iii twice a day, were given until the patient was transferred to the medical service. In accordance with our plan, after a short control period 50 mg. of thiamin chloride were administered parenterally each day. This drug was given for 33 days and supplemented for the last 15 days by brewers' yeast and cod liver oil tablets (grs. x four times a day). During this period, five electrocardiograms and two six-foot roentgenograms of the heart were taken. The electrocardiogram remained essentially unchanged and the cardiac measurements at the end of this phase of therapy were: ml. 8.8 cm., mr. 5.9 cm., total 14.5 cm.; arch 2.9 cm. (figure 2). After 20 days of thiamin therapy the basal metabolic rate was —36 per cent (figure 5).

Since there was no apparent improvement after 33 days of intensive vitamin therapy, thyroid extract was begun on January 23, 1940, the forty-eighth hospital day. The drug was first given in doses of one-half grain twice daily and the dosage was increased gradually until on February 3 (the fifty-ninth hospital day) one grain was taken three times a day.

On January 30, eight days after starting thyroid extract, T-waves had appeared in all three leads of the electrocardiogram and the QRS voltage was slightly increased. On February 16, after 25 days of thyroid medication, the electrocardiogram was essentially normal with T-waves 3 to 4 mm. in height and QRS deflections of 7 to 12 mm. On the same day, the transverse thoracic diameter was 26.4 cm., the ml. 6.8 cm.; the mr. 4.8 cm.; total 11.6 cm.; arch 2.8 cm. (figure 6). The basal metabolic rate was —8 per cent on February 9 and plus 10 per cent on February 26, the day before discharge.

Before the patient left the hospital there had been a marked amelioration of all the symptoms and signs which were previously so distressing. This change dated from the day thyroid medication was begun and all improvement prior to this time was minimal and could be ascribed to the rest and care of hospitalization. Several days after thyroid extract was begun the patient noted a sense of well being, conversed at length, and stated that her hearing had improved. Her skin gradually

became moist and soft and her hair somewhat less dry and brittle. The pitch of her voice was raised and all hoarseness and halting manner of speech disappeared. Before she left the hospital much of the yellow color of her skin had faded, although the xanthomatous nodules remained unchanged.

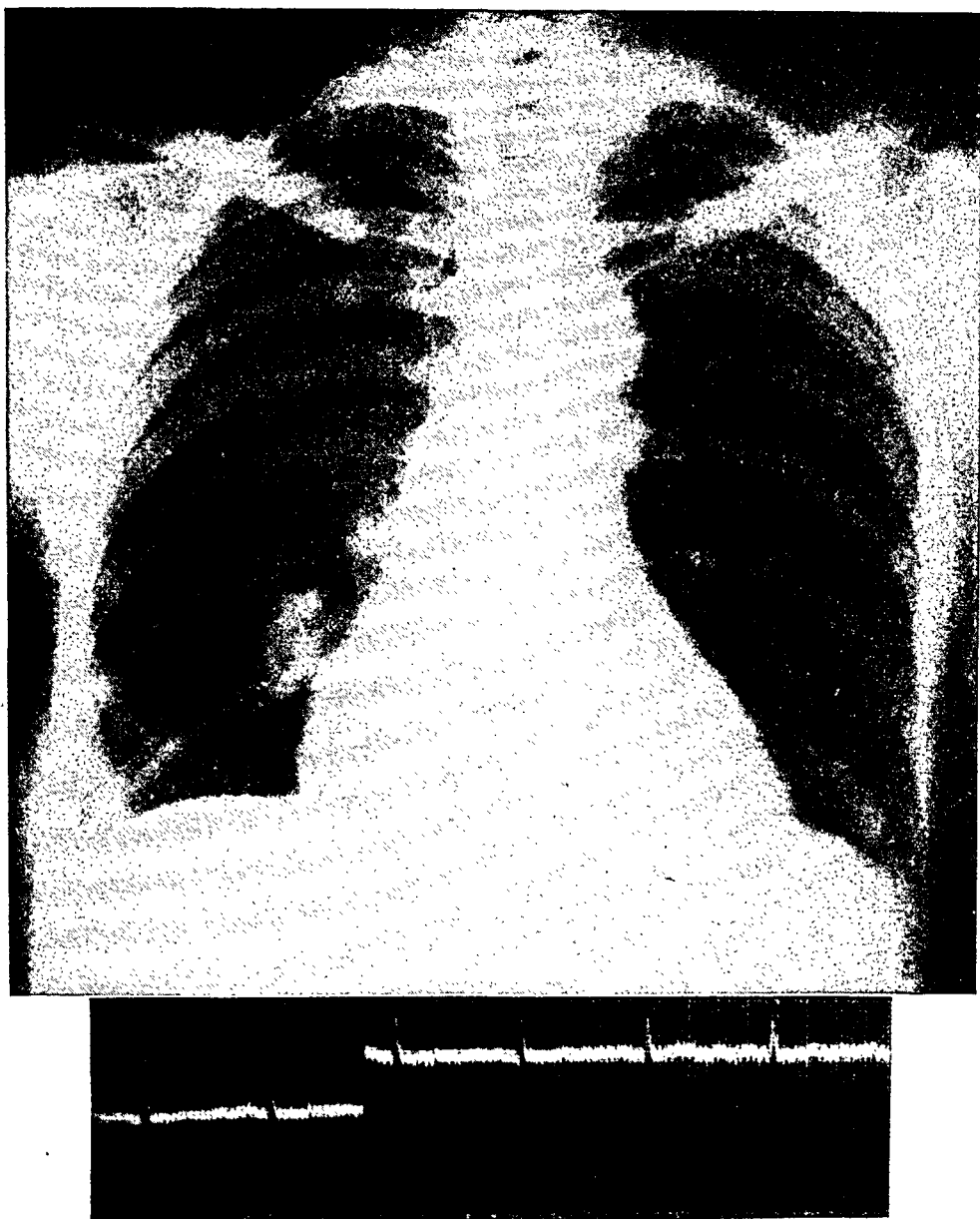


FIG. 5. Teleoroentgenogram and electrocardiogram of the same patient after 33 days of intensive vitamin B therapy (thiamin and B complex). There is no appreciable change; the slight increase in voltage of the electrocardiogram is due to improper standardization.

She was seen on several occasions in the out-patient department but had no complaints and the xanthomata of the skin appeared smaller. Several basal metabolic measurements were made, with values ranging from -8 per cent to $+10$ per cent. Thyroid extract was taken in doses of one grain three times daily. The glucose

tolerance was repeated, the fasting level was 80 mg. per cent, the peak 150 mg. per cent, and at the end of two hours the value had fallen to 85 mg. per cent. Ferrous sulfate was continued, and on April 6, 1940, the hemoglobin was 96 per cent and the red blood cells 4,300,000. The cholesterol never went above 240 mg. per cent and the cholesterol tolerance test was not repeated.

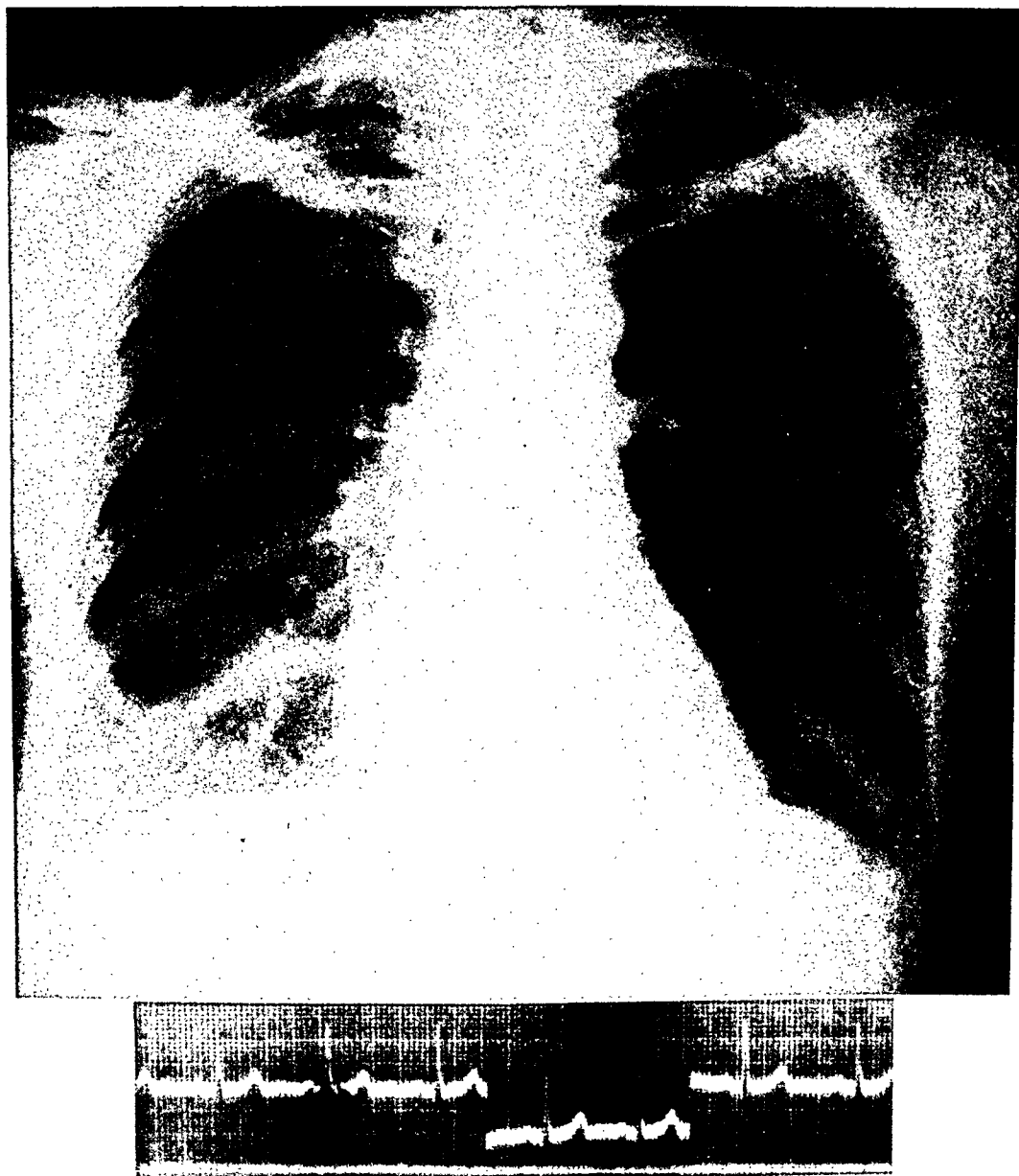


FIG. 6. Teleoroentgenogram and electrocardiogram of Patient 2. Note shrinkage in transverse diameter of the heart and prompt return of electrocardiogram to normal after 25 days of thyroid medication.

DISCUSSION

Changes in the muscle fibrils of the myxedema heart such as vacuolization, loss of striation, branching, pyknotic nuclei and irregularity of the staining properties may be found in other conditions. Wenckebach¹² and

Weiss and Wilkins¹⁴ found these changes in beriberi heart, but the latter workers, as well as Lufkin, demonstrated identical processes in the hearts of patients dying other than cardiac deaths. The writer noted a similar picture in the hearts of dogs starved seven to 21 days. There is nothing to indicate why the same pathological picture should occur in widely different conditions, but it is significant that it is the chief pathological abnormality of the myxedema heart.

In myxedema, characteristic electrocardiographic disturbances are seen, but variable tracings are obtained from the patients with beri-beri heart and non-cardiac conditions. Either identical pathological processes fail to produce typical electrocardiographic patterns or the metabolic disturbance is primarily responsible for the electrocardiogram in myxedema.

Thiamin and vitamin B concentrate, although extremely effective in the treatment of beriberi heart, completely fail to improve the myxedema heart which responds promptly to thyroid medication. Perhaps in the future some physiologic relation between the vitamins and thyroxin may be discovered, but at present the results of such investigations are controversial.

Hundhausen¹⁵ demonstrated that B_1 decreases thyrotropic and gonadotropic hormone secretion in the rat. Elmer¹⁶ showed that excessive vitamin B_1 did not diminish the action of thyroid extract. Mitchell¹⁷ proved excessive doses of vitamin B to have no effect on basal metabolism. Drill¹⁸ found that large doses both of B_1 and of B_2 given to hyperthyroid rats resulted in an increase in weight. B_1 alone did not. Löhr¹⁹ stated that vitamin B_1 deficiency symptoms and the symptoms of hyperthyroidism are strengthened by each other. Means²⁰ and Frazier and Ravdin²¹ believe that vitamin B_1 should be given preoperatively to patients with hyperthyroidism.

CONCLUSIONS

1. Hydropic vacuolization, loss of striation, branching, pyknotic nuclei and irregularity in staining properties of the muscle fibrils are seen in myxedema heart but are not specific for this entity.

2. Thiamin and vitamin B complex are ineffective therapeutic agents for myxedema heart.

BIBLIOGRAPHY

1. ZONDEK, H.: *Das Myxödemherz*, München. med. Wchnschr., 1918, lxxv, 1180.
2. FAHR, G.: Myxedema heart, Jr. Am. Med. Assoc., 1925, lxxxiv, 345.
3. ASSMANN, H.: *Das Myxödemherz*, München. med. Wchnschr., 1919, lxxvi, 9.
WILLINS, F., and HAINES, S.: Status of the heart in myxedema, Am. Heart Jr., 1925, i, 67.
4. HOLZMAN, J.: Myxedema heart, Am. Heart Jr., 1929, iv, 351.
5. HALLOCK, P.: The heart in myxedema, with a report of two cases, Am. Heart Jr., 1933, ix, 196.
5. SCHULTZ, A.: Ueber einen Fall von Athyrosis congenita (Myxödem), Virchow's Arch. f. path. Anat., 1921, ccxxxii, 302.

6. BEHR, E., and MÜLDER, J.: Het Myxoedeemhart, Een Pathologisch-Anatomische Bijdrage, Nederl. Tijdschr. v. Geneesk., 1938, lxxxii, 4303.
7. WEBSTER, B., and COOKE, C.: Morphologic changes in the heart in experimental myxedema, Arch. Int. Med., 1936, lviii, 269.
8. BROOKS, H., and LARKIN, J.: A brief experimental study of the morphology of the heart muscle following hypothyroidism, Am. Jr. Med. Sci., 1918, clv, 66.
9. OHLER, W., and ABRAMSON, J.: The heart in myxedema, Arch. Int. Med., 1934, liii, 165.
HIGGINS, W.: The heart in myxedema: correlation of physical and post-mortem findings, Am. Jr. Med. Sci., 1936, cxci, 80.
10. LUFKIN, N.: Pathologic changes in the heart in myxedema, Jr. Lancet, 1940, lx, 41.
11. CELEN, W.: Ueber Myxödem, Ziegler's Beitr., 1921, lxix, 342.
12. LUFKIN, N.: Personal Communication.
13. WENCKEBACH, K.: Das Beriberi Herz, 1934, Julius Springer, Berlin and Wien.
WENCKEBACH, K.: The riddle of beriberi heart, Libman Anniversary Vol., International Press, New York, 1932, iii, 1199.
14. WEISS, S., and WILKINS, R.: The nature of cardiovascular disturbances in vitamin deficiency states, Trans. Assoc. Am. Phys., 1936, li, 341.
WEISS, S., and WILKINS, R.: The nature of cardiovascular disturbances in nutritional deficiency states (beriberi), ANN. INT. MED., 1937, xi, 104.
15. HUNDHAUSEN, G.: Über die Beziehungen zwischen Avitaminose-B₁ und gonadotropem Hormon des Hypophysenvorderlappens, Arch. f. exper. Path. u. Pharmacol., 1939, excii, 670.
16. ELMER, A., GIEDOSZ, B., and SCHEPS, M.: Effects of increased vitamin B₁ in experimental hyperthyroidism, Compt.-rend. Soc. de biol., 1937, cxxvi, 1037.
17. MITCHELL, H., and CARMAN, G.: Effects of excessive amounts of vitamin B on basal metabolism, Biol. Abstr., 1927, i, 4693.
18. DRILL, V.: Effect of vitamin B₁ and B₂ complex on the loss of weight produced in rats by experimental hyperthyroidism, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 313.
19. LÖHR, H.: Diätetische und Vitamintherapie des Morbus Basedow, Med. Welt, 1937, xi, 111.
20. MEANS, J., HERTZ, S., and LERMAN, J.: Nutritional factors in Graves' disease, ANN. INT. MED., 1937, xi, 429.
21. FRAZIER, W., and RAVDIN, I.: The use of vitamin B₁ therapy in the preoperative preparation of the hyperthyroid patient, Surgery, 1938, iv, 680.

ABDOMINAL PAIN IN PULMONARY THROMBOSIS *

By WILLIAM S. MIDDLETON, F.A.C.P., *Madison, Wisconsin*

IN the past 16 years the antemortem diagnosis of pulmonary thrombosis has been made in 53 subjects disclosing this lesion at necropsy in the Wisconsin General Hospital. The criteria for this clinical diagnosis are familiar but frequently minimized. An analysis of these data is, therefore, undertaken before recounting the unusual occurrence of abdominal pain in pulmonary thrombosis.

The incidence of pulmonary thrombosis was much more frequent in men than in women (41 men to 12 women, a ratio of 3.4:1). The age distribution follows:

Age	Number	Per Cent
21-30	4	7.5
31-40	8	15.
41-50	11	20.9
51-60	16	30.1
61-70	7	13.2
71-80	6	11.3
-82	1	1.7

Although the dispersion is quite wide, one-half of the incidence appeared in patients between 41 and 60 years of age. In the four patients dying in the third decade (at 24, 25, 26 and 28 years respectively), the rheumatic state was the constant etiological background. In two of these, rheumatic endocarditis was the pathological diagnosis; in the third, adhesive pericarditis (rheumatic); in the fourth, *Streptococcus viridans* endocarditis lenta on a rheumatic background.

Cardiovascular lesions dominated the clinical and pathological diagnosis:

Diagnosis	Number	Per Cent
Arteriosclerotic heart disease.....	30	56.6
Rheumatic heart disease.....	12	22.6
Syphilitic heart disease.....	2	3.7
<i>Streptococcus viridans</i> endocarditis lenta.....	2	3.7
Adhesive pericarditis.....	1	1.7
Vascular nephritis.....	1	1.7

The remaining diagnoses included bronchiogenic carcinoma (2), carcinoma of the uterus (1), prostatic hypertrophy (1), and multiple abscesses of the liver (1). Included in the arteriosclerotic group were four subjects with coronary occlusion, of whom two had developed aneurysm of the left ventricle. One patient with syphilitic aortitis had an aneurysm of the aortic arch. Thirteen of the total cardiovascular group had auricular fibrillation. The functional capacity of these patients was established in this distribution:

Functional Capacity	Number	Per Cent
Grade I.....	6	11.3
Grade II.....	1	1.7
Grade III.....	4	7.5
Grade IV.....	42	79.2

* Received for publication March 26, 1942.

TEN YEARS' EXPERIENCE WITH THOROTRAST HEPATOSPLENOGRAPHY *

By WALLACE M. YATER, M.D., F.A.C.P., and FRED O. COE, M.D.,†
Washington, D. C.

ALMOST 11 years ago we began to employ thorium dioxide sol intravenously for the purpose of demonstrating radiographically the liver and spleen as first used by Radt^{1, 2, 3, 4} and Oka.^{5, 6} Since that time we have used this method of diagnosis in more than 300 patients. This figure does not include the many cases of arterial and venous disease in which we have used smaller amounts of thorotrast ‡ for angiography.

In 1933 Yater and Otell⁷ published a report of our clinical experience with 100 patients, and in 1936 Yater, Otell and Hussey⁸ reported a follow-up study of 200 patients examined over a period of five years. This third report is a follow-up study of 286 patients examined over a period of more than 10 years, whose records were obtainable.

When we began to employ thorotrast hepatosplenography we were aware of two major problems in connection with this diagnostic procedure: (1) the possibility of the effects of latent radioactivity and other serious remote ill effects, and (2) the true value, finer points, and limitations of the method. It is hoped that the present report will help in some measure to elucidate these problems. It has been accepted, we believe, that serious immediate ill effects do not occur.

In recent years a large number of articles have appeared in the medical literature condemning the parenteral use of thorotrast because of supposed latent radioactivity or because of neoplastogenic properties of thorotrast deposited in the subcutaneous tissues. Practically all of these reports are based upon animal experimentation.

In 1938, Orr, Popoff, Rosedale and Stephenson⁹ reviewed the subject and reported their experiments with rabbits. They found even minute amounts of injected tissue to be radioactive by means of histoshadowgrams and the spinthariscopes. The use of filters showed that both alpha and gamma radiation were present. All histologic changes were attributed to the presence of thorotrast, of which the main ones were lesions in the liver varying from simple cloudy swelling to profound necrosis followed by fibrous tissue proliferation, degeneration or necrosis of the lymph follicles of the spleen, and hematopoietic depression of the bone marrow. From these studies they drew the following conclusions:

* Read at the St. Paul meeting of the American College of Physicians, April 24, 1942.

From the Departments of Medicine and Radiology of the Georgetown University and Gallinger Municipal Hospitals, Washington, D. C.

† From the Radiological Clinic of Drs. Groover, Christie and Merritt.

‡ Thorotrast is the trade name given by the Heyden Chemical Company to its stabilized colloidal solution of thorium dioxide, which contains 25 per cent by volume of thorium dioxide.

1. Thorotrast is not eliminated from the body.
2. It apparently blockades the reticulo-endothelial system and may thus adversely affect a portion of the body's immunity mechanism.
3. It may profoundly damage the liver and spleen parenchyma with early and late degenerative changes.
4. It is a radioactive substance and undoubtedly has dangerous cumulative radioactive effects.

A few other articles may be mentioned as examples of the type of data upon which similar conclusions were based. In 1937 Taft,¹⁰ using the Geiger counter, pointed out that a clinical dose of 75 c.c. of thorotrast possesses the gamma-ray activity of 1.37 micrograms of radium, and that thorium dioxide breaks down into mesothorium and radiothorium. This figure was in close accordance with that stated in 1932 by the Council on Pharmacy and Chemistry of the American Medical Association.¹¹ As little as 2 micrograms of radium has produced symptoms of radium poisoning (Martland¹²). Selbie¹³ in 1938 reported that thorotrast given subcutaneously to rats and mice produced a tumor at the point of inoculation in 85 per cent of the rats and 26 per cent of the mice that lived for more than a year, spindle-cell sarcomata predominating. Foulds¹⁴ in 1939 produced one carcinoma, two sarcomata, and one fibrosarcoma in three out of nine guinea pigs by injecting 0.2 to 0.3 c.c. of thorotrast into the base of the nipple, the average induction time being 37 months, and the first three tumors being transplantable.

In 1941 Stenstrom¹⁵ reported a study of the radioactivity of the feces and breath of two patients who had received intravenous injections of 75 c.c. of thorotrast six and seven years previously and of the feces and urine of three rabbits in which 2 c.c. of thorotrast were injected into the veins of an ear, collections of urine and feces being made in the latter every few days for a long period of time. The study also included a determination of the amount of radioactivity of various organs of a rabbit which was killed 127 days after the injection of thorotrast. Radioactivity of appreciable amount was present in all specimens. Stenstrom concluded that "The presence of thorium in a living animal or patient can be revealed by means of gamma-ray measurements, but such measurements do not give quantitative values for the thorium. Thorium X is consistently found in the feces and thoron is exhaled in the breath. For quantitative determinations of the different radioactive elements in the thorium series it would be necessary to determine the range of the alpha particles and also to make beta-ray measurements. The relative amounts of the different elements depend to a certain extent upon the time elapsed since the thorium was concentrated. Excretion of thorium after intravenous injection of thorotrast in patients has not been discovered as yet and these studies show that a great portion of the thorium must have still remained in the tissues of two patients who received injections six and seven years prior to the measurements."

On the other hand, clinicians have not reported any serious ill effects as a result of the use of thorotrast. Rigler, Kouchy and Abraham¹⁶ in 1935 published a follow-up study of 175 patients, of whom 22 had had the solution injected one, two or three years before without any ill effect. Reeves,¹⁷ pointing out the value of thorotrast hepatosplenography in liver abscess in 1936, stated that in an experience of seven years he had not observed ill effects in patients. Koster,¹⁸ demonstrating in 1940 the value of this method in three cases of pylephlebitis with liver abscess, noted that he had patients alive and not showing harmful effects three, four and five years after the introduction of the medium. Yater and Whitmore¹⁹ in 1938 studied microscopic sections of the liver and spleen of 64 patients who had received thorotrast for varying periods of time before operation or death and were unable to find any evidence that the thorotrast had contributed to their death or that their organs showed damage that could be ascribed to its presence. One patient who had a nodule in the antecubital space resulting from the accidental subcutaneous injection of thorotrast more than four years before showed only a fibrous encapsulation of the thorotrast in a biopsy specimen of the tumor.

Technic of Hepatosplenography. Although thorium dioxide sol (thorotrast) has been used as a contrast medium for many purposes, it has been employed in the highest number of cases for hepatosplenography and for arteriography. For the latter purpose it has no peer. When injected into the blood stream thorotrast is removed rapidly and engulfed by the reticulo-endothelial cells throughout the body. These cells, being numerous in the liver and spleen, allow these organs to be demonstrated on roentgenograms, because thorium, a metal of high atomic weight, is radiopaque. The average dose employed by us for this purpose has been 75 c.c., given intravenously, usually in divided doses of 25 c.c. on each of three successive days, the film being made on the fourth day. However, the entire amount may be given at one time without danger, and good films may be obtained as early as one and three-fourths hours later. In 1937 Yater²⁰ showed that with this single dose of thorotrast the contrast medium is engulfed by the reticulo-endothelial cells of the liver and spleen as early as 15 minutes after the injection in sufficient amount to allow a shadow to be cast by these organs on the roentgenogram, and that films made after one and three-quarters hours show only slight improvement. Good films are usually obtainable with the patient placed in the prone position by means of the following technic: 300 M.A.; K vp. 58; distance 40 inches; time $\frac{1}{4}$ to $\frac{1}{2}$ second, depending on the size of the patient. It is important that thorotrast not be injected subcutaneously, since a hard fibrous nodule results which may become painful at times and which may make subsequent use of the vein difficult.

In good films the normal liver casts a homogeneous shadow of approximately the same density as the spine, but occasionally the normal liver shows a very fine mottling, which, however, is much more delicate than

that seen in cases of cirrhosis (figure 1). The normal spleen has a density slightly less than that of the liver and about the same as that of the ribs. Although we measure the liver and spleen in centimeters,⁷ a good idea of the relative size as compared to normal and to subsequently made films is gained by simple inspection.



FIG. 1. Normal hepatosplenogram.

Follow-up Study of 189 Patients Who Died. Of the patients who could be traced at this time 189 are known to be dead. These included 119 males and 70 females; and 104 were white patients, 84 colored patients, and 1 Filipino. At the time of injection of thorotrast seven patients were in the first decade of life, two in the second decade, seven in the third decade, 46 in the sixth decade, 40 in the seventh decade, 17 in the eighth decade, and two in the ninth decade; in two cases the ages could not be found. The majority of the patients were given 75 c.c. of thorotrast; children were given relatively smaller amounts, and some adults received 40 or 60 c.c.

In 70 cases necropsy was performed, and in a number of cases surgical coeliotomy was performed. Of the patients who came to necropsy 40 had

carcinoma or other malignant neoplasia, 17 had cirrhosis of the liver, and the other 13 had such miscellaneous conditions as myeloid leukemia, tuberculosis, disease of the heart, pernicious anemia, sickle-cell anemia, and bacterial endocarditis. The clinical diagnoses in the cases in which necropsy was not performed were cancer or other malignant neoplasia in 46, cirrhosis of the liver in 28, leukemia in eight, congestive heart failure in five, hepatitis in three, tuberculosis in three, and such miscellaneous diseases in the remaining 26 as amebic liver abscess, hemochromatosis, hepatoma, polycystic kidneys, subphrenic abscess, and ruptured spleen. All of the 189 patients had diseases serious enough in themselves to account for death, and in none could the thorotrast be in any wise considered a factor in either causing death or precipitating it.

There were 16 patients who died within 24 hours of the administration of thorotrast, 17 who died between 24 hours and one week, 51 who died between one week and one month, 49 who died between one month and six months, 14 who died at the end of a year, and 29 who lived from one year and three months to eight years and three months. In 13 cases the information available did not allow an accurate determination of the time elapsed.

Of the 29 patients who lived more than one year and three months, there were nine who lived between one and two years, eight between two and three years, four between three and four years, two between four and five years, two between five and six years, three between seven and eight years, and one more than eight years. Ten of these 29 patients had cirrhosis of the liver, and in four cases the diagnosis was verified by necropsy. These patients lived from one year and eight months to eight years and three months after the administration of thorotrast. One of them lived seven years and another eight years and three months. The one who lived seven years was 42 years old at the time of the first examination in December, 1935. He was an Italian tile setter who had noticed progressive enlargement of the abdomen for more than a year. He did not drink immoderately. He was found to have a greatly enlarged liver, and the hepatosplenogram showed the typical appearance of hypertrophic cirrhosis with a moderately enlarged spleen. A year later he was seen again. This time he was moderately jaundiced, his liver was still greatly enlarged and his spleen was then palpable. A bromsulfalein test showed 50 per cent retention at the end of 5 minutes and 15 per cent at the end of 30 minutes. The quantitative Van den Bergh test was 5 mg. per 100 c.c. of blood. The hepatosplenogram had not changed. In January 1942 this patient was hospitalized and was found to be moderately icteric and to have ascites and an enlarged liver. His hepatosplenogram showed many large rounded opaque masses within and adjacent to the liver shadow, evidently lymph nodes filled with thorotrast. He died in six weeks and necropsy revealed typical Laennec's cirrhosis of the liver. Another patient, who lived five years and one month after the administration of thorotrast, when she was 71 years old, had typical syphilitic

cirrhosis of the liver with lobulation at that time. The liver and spleen were both enlarged, and there were many large collateral veins. The necropsy revealed a small, firm, coarsely nodular liver and a moderately enlarged spleen; there was a small amount of ascites but no jaundice.

Other interesting patients in this group were one with chronic lymphatic leukemia who lived one year and six months, one with chronic myeloid leukemia who lived two years and four months, one with lymphosarcoma who lived one year and 10 months, one with carcinoma of the ampulla of Vater who lived one year and 11 months, and one with mitral stenosis who lived seven years and five months and died of subacute bacterial endocarditis.

Report of 67 Patients Who Could Not Be Traced. There were 67 patients whose records were available but who could not be traced at this time. The age, sex and color incidence were approximately the same as in the group of patients who were known to have died. It is probable that many of these untraced patients had also died, since 10 were given the diagnosis

TABLE I
Pertinent Data of 30 Rechecked Patients

Case No.	Sex	Color	Age When First Examined	Diagnosis	Number c.c. of Thorotrast	Time Since Injection	Bromsulfalein Test at Last Examination *	General Condition
1	Female	White	58	Chronic lymphatic leukemia	60	10 years, 5 months	Not satisfactory because of veins	Good
2	Male	White	60	Syphilitic aortitis	50	10 years, 6 months	Refused	Good
3	Female	White	28	Hepatitis with jaundice and ascites	60	10 years, 5 months	70% and 0%	Good
4	Male	White	37	Diabetes and carotinemia	75	10 years, 1 month	60% and 5%	Had "stroke" 1 year ago
5	Female	White	36	Syphilitic cirrhosis	75	10 years	55% and 5%	Working; had baby in 1935
6	Male	White	3	Xanthomatosis	25	10 years	10% and 5%	Well; repeated roentgen-ray treatments
7	Female	White	49	Cirrhosis	60	10 years	50% and 5%	Good
8	Male	White	25	Hemolytic jaundice	25	10 years	60% and 0%	Good but jaundiced
9	Male	White	33	Exophthalmic goiter	75?	10 years	25% and 10%	Good, drinking excessively
10	Female	White	32	Catarrhal jaundice	75	9 years, 9 months	Not satisfactory	Dementia praecox, otherwise good
11	Male	Colored	55	Syphilitic cirrhosis	75	9 years, 8 months	60% and 20%	Good but not working
12	Female	White	60	Hepatitis	75	9 years, 6 months	55% and 0%	Good
13	Female	White	5	Thrombosis of splenic vein	15	9 years, 6 months	Not done	Good
14	Male	White	49	Hepatitis	75	9 years, 3 months	70% and 5%	Moderately good
15	Female	White	9	Possibly ruptured spleen	8	9 years, 2 months	Not satisfactory because of veins	Good

TABLE I (Continued)

Case No.	Sex	Color	Age When First Examined	Diagnosis	Number c.c. of Thorotrast	Time Since Injection	Bromsulfalein Test at Last Examination *	General Condition
16	Female	White	35	Syphilitic cirrhosis	75	8 years, 9 months	Not done	Good
17	Male	White	45	Polyserositis	75	8 years	80% and 5%	Moderately good
18	Female	White	65	Suspected cancer of stomach (eliminated by operation)	75	7 years, 4 months	30% and 0%	Good
19	Male	White	42	Transient ascites	75	7 years, 3 months	Not done	Good
20	Male	White	78	Cholecystitis	50	6 years, 2 months	Not done	Good
21	Male	Colored	48	Thromboangiitis obliterans	100	6 years, 1 month	30% and 0%	Good
22	Male	Colored	56	Gangrene of foot	Not recorded	6 years	90% and 5%	Moderately good
23	Male	Colored	32	Thromboangiitis obliterans	60	5 years, 10 months	5% at end of 1 hour	Good
24	Female	White	33	Hepatitis with jaundice and ascites	75	5 years, 4 months	70% and 20%	Good
25	Female	Colored	62	Hepatitis with jaundice and ascites	75	4 years, 3 months	50% and 10%	Good
26	Female	White	43	Cirrhosis	75	3 years, 5 months	90% and 5%	Good
27	Male	White	36	Carcinoma of colon	75	2 years, 9 months	Not done	Good and working
28	Male	White	44	Amebic abscess of liver	75	Less than 1 year	Not done	Good
29	Male	White	47	Amebic abscess of liver	75	Less than 1 year	Not done	Good
30	Female	White	40	Cirrhosis?	75	Less than 1 year	30% and 0%	Bedridden from peripheral neuritis

* All bromsulfalein tests were performed by original method of injecting 2 mg. per Kg. of body weight and taking specimens of blood at intervals of 5 minutes and one-half hour, except in case 22, in which 5 mg. per Kg. were injected and blood examined at end of 1 hour.

of carcinoma, 17 cirrhosis of the liver, three leukemia, three tuberculous peritonitis, one Hodgkin's disease, two congestive heart failure, and three sickle-cell anemia. There were 13 patients in this group who had been rechecked at varying intervals since the administration of thorotrast. Among these were four cases of cirrhosis of the liver in which reexaminations had been made at intervals of one year, one year and nine months, and three years and eight months. A patient with syphilitic cirrhosis was seen two years and two months after the administration of thorotrast. Other cases were hyperthyroidism (three years), chronic myeloid leukemia (three years and four months), sickle-cell anemia (three years and nine months), appendiceal abscess (four years), abscess of the liver (four years and two months), and purpura hemorrhagica (four years and four months). A patient for whom a definite diagnosis could not be made was rechecked at the end of two years and three months.

Recheck of 30 Living Patients. At present there are 30 patients still under observation. All but four of these have been reexamined very recently; the four not examined are known to be alive and well. A tabulation of pertinent data of these cases is given in table 1. There were nine patients who were living and well (for practical purposes) 10 years or longer following the injection of thorotrast, six after nine years, two after eight years, two after seven years, three after six years, two after five years, one after four years, one after three years, and one after two years and nine months. Three patients have Laennec's cirrhosis of the liver, three have syphilitic cirrhosis of the liver, six had severe hepatitis at the time of in-



FIG. 2. Case 1. Thorotrast in subcutaneous tissues of arms 10 years and 5 months after injection.

jection of thorotrast (three with ascites), and two had recovered from amebic abscess of the liver (one following operation and one following spontaneous drainage through a bronchus).

The remarkable point concerning this series is the fact that patients who had or have had serious disease of the liver in most instances have lived longer than was anticipated and have continued in moderately good health. There were three patients who had jaundice with ascites at the time of injection of thorotrast. Many other patients in the entire series had jaundice when the medium was administered.

A point worth emphasizing is that a review of these cases showed that the patients had fewer attacks of infectious diseases including colds than individuals of the general population. There was certainly no evidence

that the presence of thorotrast in the reticulo-endothelial cells depressed the immunity mechanism of the body.

ILLUSTRATIVE CASES

Case 1. Miss M. B. C., now aged 69 years, was found to have chronic lymphatic leukemia in July, 1930. The first hepatosplenogram was made on July 16, 1931, following the injection of 60 c.c. of thorotrast. Roentgen-ray therapy caused the blood picture to return to normal, and she has required such therapy only once since then. She has remained well to date (December 11, 1941), 10 years and 9 months,



FIG. 3. *Case 1.* Original hepatosplenogram made July 16, 1931, showing Riedel's lobe, moderately enlarged spleen, and well shown kidneys (chronic lymphatic leukemia).

with only an occasional upper respiratory infection and minor complaints. The white blood cell count is 19,900 per cu. mm. of blood with 51 per cent lymphocytes but no blast forms. Some of the thorotrast was injected accidentally in the subcutaneous tissues of both arms, causing nodular swellings. These are firm and unsightly but the patient refuses to have them excised (figure 2). They have not enlarged. The original hepato-splenogram showed some enlargement of the liver and moderate enlargement of the spleen (figure 3). The last film, made on April 17, 1942, shows

the liver to be somewhat smaller, homogeneous, but of moderately reduced density (figure 4). The spleen is about the same size and less dense. A small lymph node containing thorotrast is visible on the right side of the first lumbar vertebra; it was first observed in April, 1935.

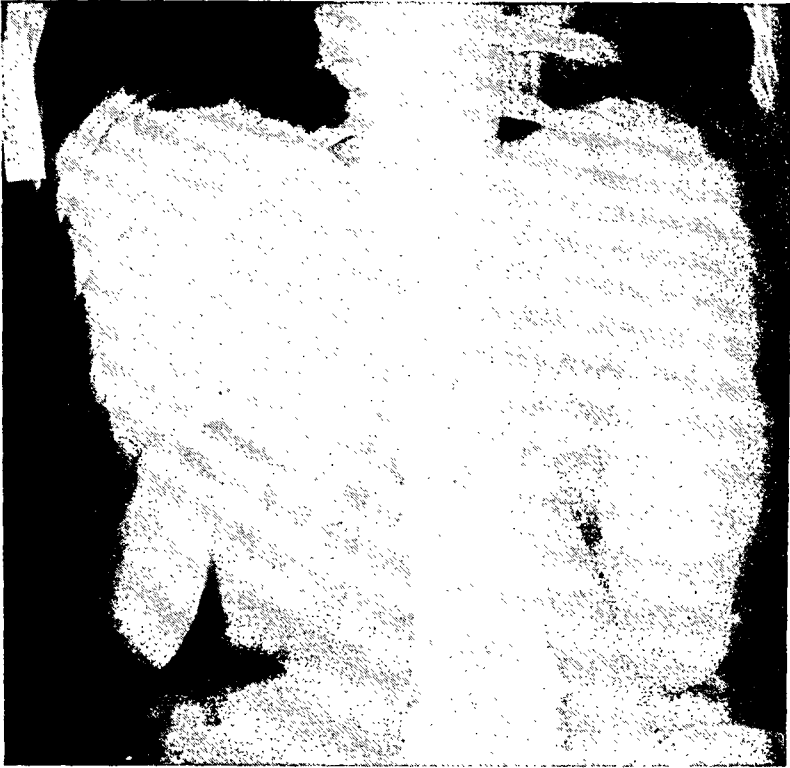


FIG. 4. *Case 1.* Hepatosplenogram made 10 years and 9 months after the first, showing moderate diminution in density of liver and spleen but no change otherwise except for a small opaque lymph node between liver and spine.

Case 2. Mrs. I. D., now aged 59, had hepatitis with severe jaundice for several weeks in November, 1931. Biopsy of the liver showed a chronic fibrosing process with a superimposed acute one characterized by large areas of leukocytic infiltration. A bromsulfalein test of liver function after recovery from the acute hepatitis showed 50 per cent retention after five minutes and none at the end of 30 minutes. On February 4, 1932, after injection of 60 c.c. of thorotrast, hepatosplenograms showed the liver to be quite small, the medium well concentrated, and no apparent alteration of structure. The left lobe was large, compared with the right. The spleen was normal in size and density. Except for various intermittent complaints, such as dyspepsia and headaches and a rare "cold," she had been well, and physical examination on May 24, 1937, was essentially negative. A liver function test performed on October 10, 1936, gave results identical with the original one. A hepatosplenogram, made May 24, 1937, more than five years after the first showed the liver and spleen to be about the same size as originally but there was great mottling and moderate reduction in density of both organs, indicative of elimination of the contrast medium, and very dense shadows of upper abdominal lymph nodes to which the mobilized thorotrast had migrated. The last check-up was made on February 12, 1942, just 10 years after the injection of thorotrast. She had continued to be well except for minor complaints and a sore near the base of the tongue. A bromsulfalein

test showed 50 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. A hepatosplenogram shows slightly less density of the liver than originally with mottling due to mobilization of the thorotrast, and dense lymph nodes in the region of the porta hepatis (figure 5). The left lobe appears to be larger than the right. The spleen is dense and perhaps a little smaller.

Case 3. M. A., a white woman now 38, had a prolonged illness in the fall of 1931 accompanied for a while by severe jaundice and ascites which gradually disappeared. Biopsy of the liver showed a subacute inflammatory process. After recovery, the bromsulfalein test showed 75 per cent retention in five minutes and 15 per cent in 30 minutes. Hepatosplenograms made December 10, 1931, after injection of 60 c.c. of thorotrast, showed the liver and spleen to be of normal size, but the liver was finely mottled. Physical examination on April 2, 1937, was essentially negative. She had gained 20 pounds. The liver function test showed 35 per cent retention in five minutes and none after 30 minutes. The hepatosplenogram showed linear and granular mottling of the liver and spleen, indicative of mobilization of thorotrast, and visible lymph nodes between the two organs. The patient has continued to be well and is getting fatter. The last physical examination made on March 13, 1942, more than 10 years after the injection of thorotrast, was negative. A bromsulfalein test showed 70 per cent retention at the end of five minutes and none at the end of 30 minutes. A hepatosplenogram looks the same as formerly with somewhat less density of the liver and spleen (figure 6).

Case 4. Mr. F. S., now aged 47, was found to have diabetes mellitus in 1931. Dietetic treatment caused carotinemia. Hepatosplenograms made on February 6, 1932, after injection of 75 c.c. of thorotrast, showed normal hepatic and splenic shadows. The patient has been very well. Hepatosplenograms made on May 24, 1937, more than five years after the first, showed some diminution in density and mottling of the liver and spleen, and lymph nodes were visible in the upper abdomen. Since then the patient has been well except for a stroke in 1937 with residual hemiparesis. Examination on March 6, 1942, more than 10 years after the injection of thorotrast, was otherwise negative. A bromsulfalein test showed 60 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. The hepatosplenogram shows somewhat less density.

Case 5. Miss L. B., now aged 18, was run over by an automobile on November 30, 1932, suffering shock and severe pain in the upper left quadrant of the abdomen. To determine whether the spleen was ruptured 8 c.c. of thorotrast were injected and a hepatosplenogram made three hours later. This showed the spleen to be intact. Recovery ensued without a surgical operation. The patient has remained well and developed normally. A hepatosplenogram made on May 3, 1937, showed very dim shadows of the liver and spleen with diffuse granular mottling of the latter and visible lymph nodes near the porta hepatis. Some thorotrast had been accidentally injected into the subcutaneous tissues of both arms and small firm nodules had resulted. These did not cause trouble and were painful only when the arm was squeezed. One was removed for microscopic study and was found to be composed of dense hyaline connective tissue encapsulating clumps of thorotrast. This patient has remained well, and a hepatosplenogram made on February 25, 1942, more than nine years after the injection of thorotrast, shows very little contrast medium in the liver, but the spleen is about as dense as on the previous examination.

Case 6. Mrs. D. M., now aged 46, was found to have syphilis 22 years ago, and treatment has been given intermittently since that time. Dyspepsia developed, and in January, 1931, the liver and spleen were found to be enlarged. In October, 1932, the liver was considerably enlarged, firm and irregular; the spleen was also moderately enlarged. A bromsulfalein test showed 45 per cent retention at the end of five minutes and none after 30 minutes. Hepatosplenograms made on March 22, 1932,



FIG. 5 (above) *Case 2.* Hepatosplenogram made 10 years after injection of 60 c.c. of thorotrast in a case of cirrhosis of the liver, showing the rather small right lobe and the enlarged left lobe of the liver which is mottled because of mobilization of thorotrast. The spleen is not enlarged but is quite dense; an accessory spleen is shown. A large group of lymph nodes containing thorotrast is demonstrable.

FIG. 6 (below) *Case 3.* Hepatosplenogram made more than 10 years after the first which was made following recovery from an attack of jaundice with ascites. Shadows are somewhat decreased in density, spleen is mottled, and adjacent lymph nodes are shown.

after the injection of 75 c.c. of thorotrast, showed the typical picture of hepar lobatum with splenomegaly (figure 7). In October, 1935, she delivered a normal baby. She has been working since then, but she has frequent nosebleeds and tires easily. On May 19, 1937, the physical examination was essentially the same as in 1932. The liver function test showed 50 per cent retention after five minutes and 5 per cent after 30 minutes. Wassermann and Kahn tests of the blood were strongly positive. The hepatosplenogram showed extensive, irregular coarse mottling of the liver due to mobilization of the contrast medium, many visible lymph nodes in the



FIG. 7. Case 6. Hepatosplenogram made on March 22, 1932, after injection of 75 c.c. of thorotrast, showing mottled and lobulated liver (hepar lobatum) with splenomegaly.

upper abdomen, and still considerable density of the enlarged spleen. In 1941 the patient became weak and very anemic because of excessive uterine bleeding. Menopause was induced by irradiation and blood transfusions and iron given in December, 1941. In January, 1942 she returned to work. The physical examination is the same as formerly. A bromsulfalein test showed 55 per cent retention at the end of five minutes and 5 per cent at the end of 30 minutes. A hepatosplenogram, made 10 years after the first, appeared the same as in 1937 (figure 8).

Case 7. Mrs. G. B., now aged 70, had a severe attack of jaundice in April, 1932. Cholecystostomy was performed, followed by recovery. A hepatosplenogram, made May 7, 1932, after injection of 75 c.c. of thorotrast, showed normal hepatic and splenic shadows. The patient has been well since then except for minor ailments. The last hepatosplenogram, made December 1, 1941, nine and a half years after the first, shows some diminution in density of the liver and spleen with mottling and visible

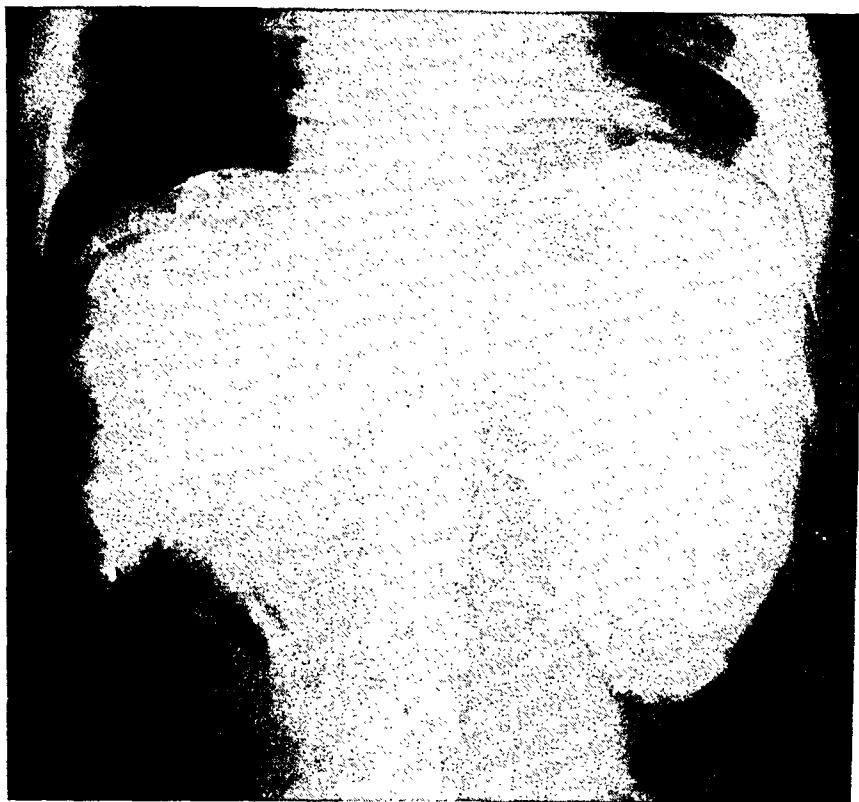


FIG. 8 (above) *Case 6.* Hepatosplenogram made December 1, 1941, nearly 10 years after the first, showing gross and irregular mottling of the liver due to the mobilization of thorotrast. Many lymph nodes containing mobilized thorotrast are visible. The spleen is still enlarged and quite dense.

FIG. 9 (below) *Case 12.* Hepatosplenogram of a case of syphilitic cirrhosis of the liver made 9 years and 8 months after injection of 75 c.c. of thorotrast, showing irregularity of liver outline and irregular mottling. The spleen is of reduced density and not enlarged. Periportal lymph nodes are visible.

lymph nodes in the upper abdomen. A bromsulfalein test on March 18, 1942 showed 55 per cent retention at the end of five minutes and none after 30 minutes.

Case 8. E. C., a white boy, now aged 13, was found to have xanthomatosis in 1931. A hepatosplenogram made on March 24, 1932 after injection of 25 c.c. of thorotrast, showed normal shadows for liver and spleen. Under roentgen-ray therapy he has improved greatly. A hepatosplenogram made on February 17, 1942, nearly 10 years after the first, shows considerable diminution in density of the liver and spleen with mottling and a visible lymph node near the porta hepatis.

Case 9. J. C., a white man, now aged 72, was first examined in September, 1931. He had syphilitic aortitis, and because of an enlarged spleen a hepatosplenogram was made (Sept. 8, 1931), after the injection of 50 c.c. of thorotrast. This showed a normal liver. He has remained well, receiving antisyphilitic treatment. Examination on March 5, 1942, showed merely aortic regurgitation. The spleen was not palpable. A hepatosplenogram, made 10 and a half years after the first, shows the spleen to be slightly enlarged; both the liver and spleen are finely mottled, and there is a small amount of thorotrast in the adjacent lymph nodes.

Case 10. F. E., a white man, now aged 43, was found to have exophthalmic goiter in 1932. A hepatosplenogram was made on March 25, 1932, after the injection of 75 c.c. of thorotrast with the idea of determining whether in this disease the spleen was contracted. The film was normal. Ten years later the patient, who had had a subtotal thyroidectomy, was found to be well, although he had become a moderate alcoholic. A bromsulfalein test showed 25 per cent retention after five minutes and 10 per cent at the end of a half hour. The hepatosplenogram shows the liver and spleen to be of normal size. Only a small amount of thorotrast seems to be retained in these organs, but there is the usual concentration of it in the adjacent lymph nodes.

Case 11. B. C., a white woman, now aged 42, had catarrhal jaundice in 1932. A hepatosplenogram made on June 1, 1932 showed the liver to be normal and the spleen moderately enlarged. She later developed dementia praecox, but remained well otherwise. Reexamination on March 14, 1942, after nine years and nine months, showed the usual changes in distribution of the thorotrast.

Case 12. J. G., a colored man, now aged 65, had jaundice, ascites, and an enlarged liver in 1932. A hepatosplenogram made on June 16, 1932 after the injection of 75 c.c. of thorotrast showed questionable evidence of syphilitic cirrhosis. The patient has remained well except for the development of diabetes mellitus. He has received antisyphilitic treatment. A physical examination on February 10, 1942 was negative, and a bromsulfalein test showed 60 per cent retention at the end of five minutes and 20 per cent at the end of 30 minutes. The hepatosplenogram, made nine years and eight months after the first, shows a lobulated liver with irregular distribution of the thorotrast (figure 9). The medium is concentrated in the splanchnic lymph nodes. The spleen is faintly visible and is normal in size.

Value of Hepatosplenography in Diagnosis. As the years have passed we have become more conservative in the use of this method of diagnosis because of better selection of cases. During the first few years we were attempting to learn all we could about it and were using it in all cases of hepatomegaly, splenomegaly, and undetermined masses in the upper abdomen, and in cases of suspected cirrhosis or possible metastases to the liver. Experience has shown that it is of little value in cases of splenomegaly. Its greatest usefulness is in helping to diagnose early cases of cirrhosis of the liver, metastases in the liver, and abscess of the liver. In the series reported there

were four cases of solitary abscess of the liver, all positively diagnosed by hepatosplenography (figure 9). Cirrhosis and metastases have been confirmed many times by this method of diagnosis. Cirrhosis of the liver is indicated by diffuse mottling or reduced density of the liver, often with changes in size or configuration of the organ. Metastases in the liver are denoted by rounded areas of lessened density surrounded often by a halo of increased density. Abscess produces a rounded area of reduced density, usually without the halo.

Little help has been obtained from follow-up films. The usual change is diffuse punctate or interlacing linear mottling and opacity of upper abdominal lymph nodes due probably to migration of Kupffer cells laden with thorotrast from the liver and spleen to their adjacent lymph nodes. In a few cases some of the thoracic lymph nodes have shown evidence of thorotrast deposition. In one case it appears as if there is thorotrast in both hemidiaphragms. In only three cases has the spleen become importantly reduced in size with increased density. In some cases of cirrhosis of the liver that organ has become smaller. In comparing films, due consideration must be made for even slight differences in technic.

As to the correctness of diagnosis by hepatosplenography, review of our 286 cases shows that the diagnosis of conditions of the liver was correct or very probably correct in 159 instances, incorrect in 10, and unsatisfactory (because of technical or other difficulties) in 25; in 92 cases it was impossible to verify the diagnosis by necropsy, operation or subsequent course.

SUMMARY AND CONCLUSIONS

A report has been made of the use of thorotrast hepatosplenography in 286 cases over a period of more than 10 years. Of these patients 10 were known to have lived for more than 10 years, 5 between 9 and 10 years, 3 between 8 and 9 years, 5 between 7 and 8 years, 3 between 6 and 7 years, 4 between 5 and 6 years, 6 between 4 and 5 years, 10 between 3 and 4 years, 10 between 2 and 3 years, and 12 between 1 and 2 years. No immediate or remote ill effects of importance have been observed. There has been no evidence of latent radioactivity, depression of hepatic or splenic or hematopoietic function, lowered resistance to infection, or development of malignant neoplasia at the site of injection.

Hepatosplenography is of definite value (1) in helping to diagnose cirrhosis of the liver, (2) to determine the presence of metastases in the liver, and (3) in the diagnosis of abscess of the liver.

Care should be taken to inject thorotrast into the veins and not into adjacent tissues, not because of the possibility of the development of neoplasms, but in order to prevent the formation of nodules and to save the veins.

The authors wish to express their gratitude to Dr. Richard H. Meredith, fellow in medicine, Dr. Philip S. Arthur, fellow in radiology, and Mrs. Alice Eldred Bond, secretary, for their assistance in accumulating records and films and reexamining patients.

BIBLIOGRAPHY

1. RADT, P.: Eine Methode zur röntgenologischen Kontrastdarstellung von Milz und Leber, *Klin. Wchnschr.*, 1929, viii, 2128-2129.
2. RADT, P.: Über die körnige Ablagerung colloider Farbstoffe in den Leberparenchymzellen von Kanninchen nach intravitaler Injektion (nach Versuchen mit Tusche und Eisen), *Ztschr. f. d. ges. exper. Med.*, 1930, lxi, 721-741.
3. RADT, P.: Zur röntgenologischen Kontrastdarstellung von Leber und Milz, *Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong.*, 1931, xliii, 443-451.
4. RADT, P.: Eine Methode zur röntgenologischen Sichtbarmachung von Leber und Milz durch Injektion eines Kontrastmittels (Hepato-Lienographie), *Med. Klin.*, 1930, xxvi, 1888-1891.
5. OKA, M.: Eine neue Methode zur röntgenologischen Darstellung der Milz (Lienographie), *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1929, xl, 497-501.
6. OKA, M.: Klinische Anwendung der "Lienographie" einer neuen Methode zur röntgenologischen Darstellung von Milz und Leber, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1930, xl, 892-898.
7. YATER, W. M., and OTELL, L. S.: Hepatosplenography with thorium dioxide sol: clinical experience with one hundred patients, *Jr. Am. Med. Assoc.*, 1933, cl, 507-514.
8. YATER, W. M., OTELL, L. S., and HUSSEY, H. H.: Hepatosplenography with stabilized thorium dioxide sol: a follow-up study of 200 patients examined over a period of five years, *Radiology*, 1936, xxvii, 391-409.
9. ORR, C. R., POPOFF, G. D., ROSEDALE, R. S., and STEPHENSON, B. R.: A study of the effect of thorium dioxide sol injected in rabbits, *Radiology*, 1938, xxx, 370-381.
10. TAFT, R. B.: The radio-activity of thorium dioxide sol, *Jr. Am. Med. Assoc.*, 1937, cviii, 1779-1781.
11. Report of Council on Pharmacy and Chemistry: Thorotrast, *Jr. Am. Med. Assoc.*, 1932, xcix, 2183-2185.
12. MARTLAND, H. S.: The occurrence of malignancy in radioactive persons, *Am. Jr. Cancer*, 1931, xv, 2435-2516.
13. SELBIE, F. R.: Tumors in rats and mice following the injection of thorotrast, *Brit. Jr. Exper. Path.*, 1938, xix, 100-107.
14. FOULDS, L.: The production of transplantable carcinoma and sarcoma in guinea pigs by injections of thorotrast, *Am. Jr. Cancer*, 1939, xxxv, 363-373.
15. STENSTROM, W.: Elimination of radioactive elements of patients and rabbits after injection of thorotrast, *Radiology*, 1941, xxxvii, 698-704.
16. RIGLER, L. G., KOUCHY, R., and ABRAHAM, A. L.: The effects of thorium dioxide sol (thorotrast) on the human liver, *Radiology*, 1935, xxv, 521-532.
17. REEVES, R. J.: The use of thorium dioxide in the roentgenographic study of liver abscess, *Am. Jr. Roentgenol.*, 1936, xxxvi, 923-927.
18. KOSTER, H.: Thorium dioxide as an aid in the differential diagnosis of pylephlebitis, *Radiology*, 1940, xxxv, 728-734.
19. YATER, W. M., and WHITMORE, E. R.: Histopathologic study of tissues of 65 patients injected with thorium dioxide sol for hepatosplenography, *Am. Jr. Med. Sci.*, 1938, cix, 193-205.
20. YATER, W. M.: Rate of deposition of thorotrast in the human liver and spleen, *Am. Jr. Roentgenol.*, 1937, xxxviii, 447-449.

A RECORDING SPHYGMOTONOGRAPH: A MACHINE FOR THE CONTINUOUS RECORDING OF SYSTOLIC AND DIASTOLIC ARTERIAL PRESSURE IN MAN*

By KURT LANGE, M.D., *New York, N. Y.*

IN nearly all branches of medicine the problem of continuously recording the human blood pressure arises from time to time. There are many perplexing problems; the solution of which would be materially furthered by having a continuous record of the variations in systolic and diastolic pressure. In 1928 we were confronted with the following question: does the blood pressure rise, in certain types of angina pectoris attacks, prior to the attack and thereby become a provocative factor of coronary insufficiency, or does the rise merely represent a consequence of the pain and the anxiety? The answer to this query depended upon the ability continuously to follow the pressure changes occurring over long periods of time. Moreover, for years there have been demands for such a device on the part of anesthetists,¹ surgeons,² and gynecologists who desired to obtain a better impression of the changes occurring during the whole course of the preoperative, operative and the postoperative periods. Psychiatrists³ and psychologists⁴ also have desired to estimate the influence of psychic emotions on pressure changes over long periods of time.

It was the aim of our experiments to devise an instrument which would give correct and continuous records of the systolic as well as the diastolic blood pressure and which would not need an expert operator nor result in tracings which required further interpretation. The machine should be universally applicable without adjustments.

After four years of experiments, we published our first report on such an apparatus.^{5, 6} The principle of this device can be summarized as follows (figure 1):

A double-bag cuff, with a total width of 12 cm. for both bags, is applied to the arm of the person being examined. The cuff is connected to a supply of compressed gas. This connection can be interrupted electrically by a solenoid pinching valve, thus interrupting the ascent of pressure in the cuff. The lower bag of the cuff, which is connected to the upper through a very narrow orifice, has another opening leading into a nozzle, through which the air from the lower bag can blow against an instrument which transforms the puffs of air into equivalent "puffs" of current. These electric currents, sent through an amplifier or a system of sensitive relays, are used to

* Received for publication February 5, 1942.

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals and Metropolitan Hospital Service.

open or close the above mentioned solenoid valve. Since there is a small leak in the line to the upper cuff, some air can always escape from the system.

The principle of the measuring process is the following:

The device is switched into the diastolic position in which the solenoid valve is normally *open* until it is energized; then an impulse from the lower cuff appears and causes its closure. In the region below the diastolic pressure, for reasons to be explained further on, no impulse will occur from the lower cuff. When the diastolic pressure is reached, the first impulse of sufficient steepness occurs in the lower cuff; this activates the detecting

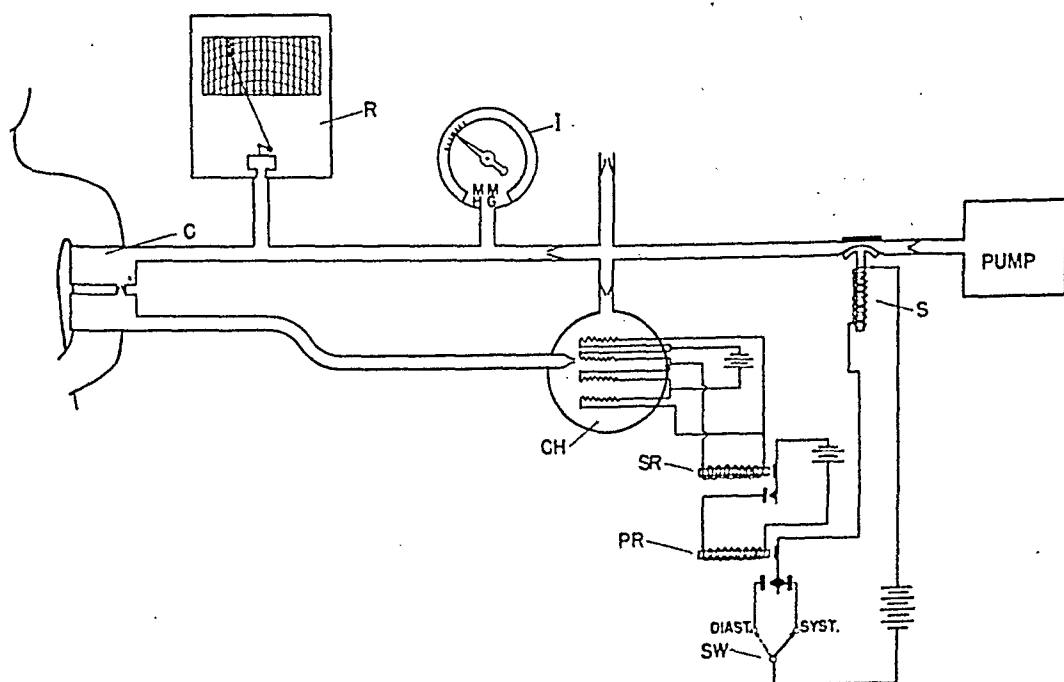


FIG. 1. Principle of the sphygmotonomograph. S = solenoid pinching valve, I = indicating instrument, R = recorder, C = double cuff, Ch = chamber containing the set of nickel coils, SR = sensitive relay, PR = power relay, SW = diast.-syst. switch.

instrument causing the solenoid valve to close, so that no compressed gas is now supplied to the cuff. This permits some air to escape through the leak and the pressure in the system to fall until a level is obtained at which no further impulses occur. Since, at this point, there is no activation of the valve, the valve automatically opens and again compressed gas is supplied to the cuff system, thus repeating the procedure. A recording and an indicating instrument are connected with the line leading to the upper cuff, giving a continuous tracing of the changes in pressure. If a systolic recording is desired instead of the diastolic, the switch is thrown over into the systolic position; in this position the solenoid valve is normally closed and opens only when an impulse is given to the sensitive instrument from the lower cuff. In the region between the diastolic and the systolic pressure every pulse causes such an impulse and thereby opens the valve and allows

compressed gas to enter the cuff system. The moment the peak of the systolic pressure has been passed, further impulse ceases, the valve closes automatically, and the leak slowly releases the pressure. When the first pulse reappears in the lower bag of the cuff, an impulse again opens the valve and allows pressure to enter the cuff, until once again impulses to the lower cuff are eliminated. This procedure, too, is recorded and indicated by the instruments.

Since our original publication, this basic principle has been applied and copied, with more or less success, by a great number of other investigators.

In 1920, unknown to us, Kolls⁷ had employed a somewhat similar idea to record the systolic pressure alone. His system had some of our features, but the lower cuff in his device was always fixed at a constant pressure of about 100 mm. Hg. The chief disadvantage of his method resides in an inability to obtain readings of the diastolic pressure and to follow fluctuations of the systolic pressure which go below 100 mm. Hg, in which case his lower cuff acted as an occlusive cuff and ceased to act as an oscillation indicator. Furthermore, the impulses from his lower cuff were transmitted to a simple contact instrument by a tambour, a system which we tried but soon abandoned on account of its unreliability.

Koch and Simon⁸ tried a procedure absolutely different from ours. They put the arm into a plaster of Paris cast and placed a rubber balloon in the hand of the patient. Fluctuations of the blood pressure were recorded from this rubber bag which was filled with compressed gas.

In 1936 Omberg⁹ altered our principle by using a microphone to activate the solenoid valve through an amplifier as soon as a sound distal to the cuff appeared or disappeared. We already had rejected this device several years prior to this time because of the difficulty in placing the microphone on the correct point and because of the high disturbance level of such a microphone when it is sufficiently sensitive to register the first faint sounds. Since it is often very difficult, even for the trained ear, to decide which is the first actual sound caused by a pulse wave passing under the cuff, a microphone, with no possibility of selection, very often gives misleading results.

In 1937 Stokvis¹⁰ copied our device in all its details save for a simple contact set-up, and reported that he obtained satisfactory results with it. We cannot understand how absolutely exact diastolic readings can be obtained by a simple contact instrument for the transformation of impulses from the lower cuff into activating currents. Moreover, a container connected to the upper cuff for the purpose of reducing the shock-like action of the device naturally must make it less accurate. Stokvis changed the instrument's former name "Autotonograph," to "Tensograph."

In the same year Darrow⁸ also used our device for psychological investigations and obtained good results.

In 1939 Doupe, Newman and Wilkins¹¹ used the same principle to record the systolic blood pressure, replacing the contact instrument for the transformation of the impulses into electric current by a mirrored tambour,

which deflected a light beam against a photocell; this measure was intended to avoid contact difficulties.

We utilized a similar system in 1935, but abandoned it, because it was not sufficiently selective for registration of the diastolic pressure.

Many investigators have published papers on the results obtained by the use of our original machine. Von Diringshofen¹² employed the machine in collaboration with the German Air Force to investigate pressure changes during power dives and tail spins under actual flying conditions. A copy of a record taken with the machine by him is shown in figure 11. Poeck¹³ investigated the influence of evipal anesthesia on the blood pressure. Kronfeld, Mueller and Reiner⁴ did extensive investigations of the influence of excitement and nervous unrest on the blood pressure. Groedel and McClellan¹⁴ and Peemoeller and Lund¹⁵ examined the behavior of the blood pressure during carbon dioxide baths. Reiner¹⁶ studied the influence of cross examinations on the blood pressure of criminals; Fasshauer and Oettel¹⁷ investigated the changes in blood pressure occurring during changes in posture on a tilting table; Von Bergmann¹⁸ reported the influence of excitement on the blood pressure of thyreotoxic patients.

The use of a simple mechanical contact instrument was unsatisfactory for obtaining absolutely accurate readings of the diastolic pressure, although the systolic tracings conformed well with the values found with the Korotkov method. However, as always stressed, changes in magnitude of the spikes obtained while inflating a cuff are not a reliable sign of the diastolic pressure. No mechanical instrument can be used for the registration of the oscillations at the diastolic point, since the diastolic reading always would depend on the magnitude of the oscillations. Furthermore, the instrument is intended to test pilots under actual flight conditions. For this reason it must be entirely insensitive to sudden accelerations, a requirement which is never fulfilled by a mechanical contact instrument. It was, therefore, advisable to replace the original contact instrument and its later modification, the light beam-photo cell device, by a system of heated wires, whose electric conductivity was sensitive to air cooling.

The puffs, originating in the lower cuff, blow against one coil of a Wheatstone bridge, thus causing an imbalance. The bridge consists of four electrically heated coils of wire with a high temperature coefficient of resistance. Nickel was used for this purpose.

The current, which now flows from the unbalanced bridge, energizes a sensitive relay which activities a power relay which, in turn, directs the solenoid valve. The response of such a bolometer, as the heated wire bridge is technically called, depends only upon the speed of the air flow directed against its coils and not primarily upon the duration or magnitude of the air stream. In a series of experiments, which will be published in another paper, it was determined that the characteristic of the oscillometric curve for the diastolic blood pressure is a sudden change in steepness of the ascending branch of each wave at the moment when the arterial wall begins to

flutter. The same finding was made by Bazett, Laplace and Scott¹⁹ in their investigation of the oscillometric criteria of the diastolic blood pressure. Since the bolometer is highly sensitive to changes in air speed, a point could easily be selected, by gradually shunting the sensitive relay, which would

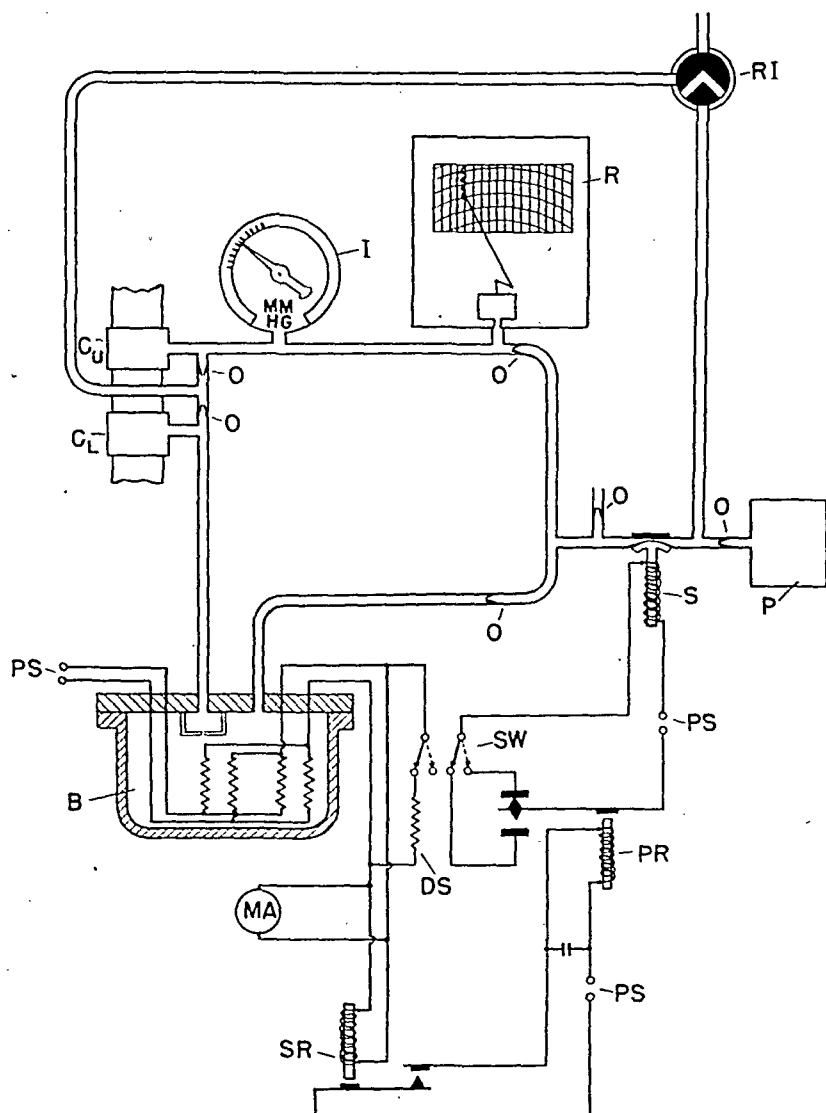


FIG. 2. Actual design of the sphygmotograph. P = pump. O = orifices. S = solenoid pinching valve. I = indicating instrument. R = recorder. C_u = upper cuff. C_l = lower cuff. B = bolometer. SR = sensitive relay. PR = power relay. DS = diastolic shunt. SW = diast.-syst. switch. R.I. = pet cock for rapid inflation and deflation of the cuff.

correspond with the sudden change in steepness of the oscillometric curve occurring at the diastolic pressure.

This bolometer was placed in a chamber which was kept at the same pressure as both bags of the cuff, by using orifices in the air supply lines to the cuff and the bolometer chamber, which are proportional to their respective

sizes. By this arrangement (figure 2) only the puffs resulting from pulse oscillations against the lower cuff, which is on the same pressure level as the upper cuff, act against the bolometer, while all fluctuations of ascending or descending air pressure in the whole system do not influence the "pulse detector" at all. At the same time the two-bag system prevents the border beats from reaching the lower cuff.

In order to avoid a shock-like operation of the machine, a condenser is inserted across the contact of the sensitive relay. The condenser is charged by every contact which this relay makes. The size is such as to keep the

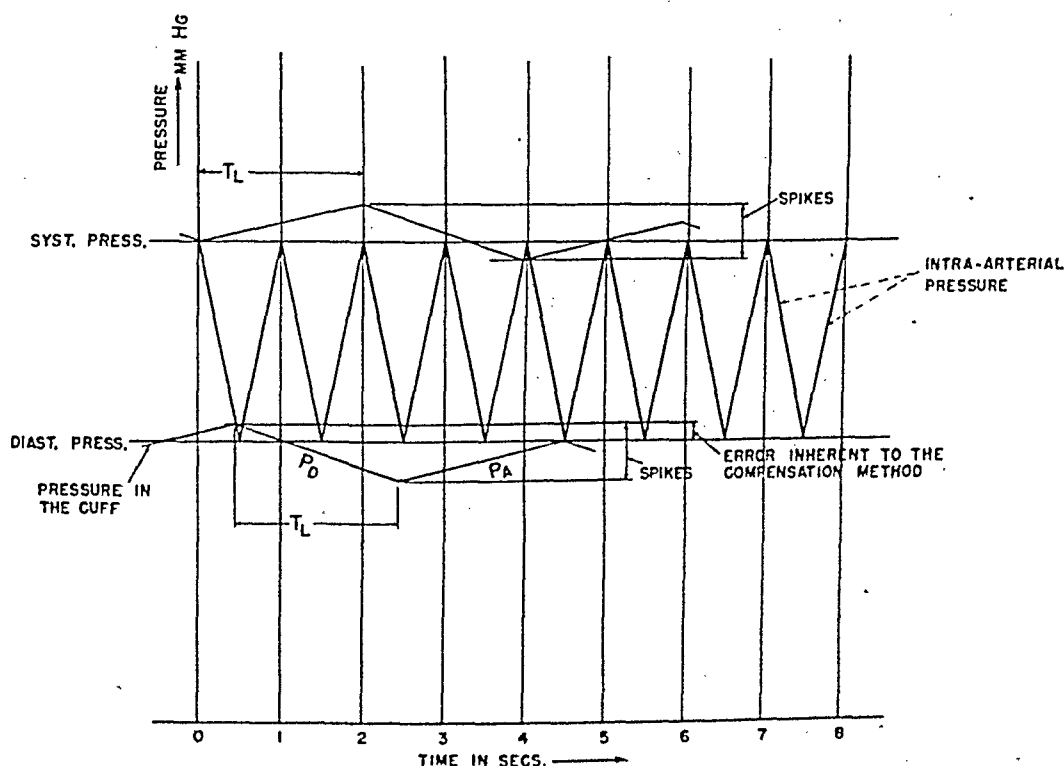


FIG. 3. Scheme of action of the sphygmotonograph. The interarterial fluctuations of the blood pressure are only sketched. t_l = duration of the time lag, p_d = speed of deflation of the cuff, p_a = speed of inflation of the cuff.

power relay closed and the pinching valve open or closed, depending on the position of the switch, for the time of two seconds after one impulse has occurred. If, in this period of two seconds, another contact occurs, a new time lag of two seconds is added. If not, the power relay breaks after two seconds, as explained in figure 3. The time lag of two seconds was chosen in order to bridge from one pulse to the next, even in cases of heart block with only 30 pulses per minute.

The pulse rate can be counted from the oscillations made by the pointer of the indicating instrument which is connected to the upper cuff and which, therefore, receives the oscillations of the border beats even when the systolic pressure is reached. When a diastolic reading is taken, the pulse rate can also be seen at the pointer of the millimeter, which shows roughly the

currents coming from the bolometer. At the same time this instrument permits the resetting of the bolometer to zero if this point should have been lost. A variable resistor across one of the bolometer coils permits this resetting; however, this is very rarely necessary.

A small, built-in motor driven compressor provides the whole device with the necessary amount of compressed air. In order to make the instrument explosion proof for its use in the operating room, it was housed in a heavy metal casing. The compressor draws its air supply through a 12 foot tube. The electric cord also runs through this tube, distant from the field of explosive gases in the operating room. Rapid inflation of the cuff can be affected through a rapid inflating valve which connects the compressor directly to the cuff, avoiding the slow ascent through the orifices in case a rapid start for the tracing of the systolic pressure seems desirable. The same by-pass can be used in another position for rapid deflation of the cuffs after the examination is finished or when it is interrupted.

The device is very simple to use. The cuff is applied snugly and high up on the arm of the patient. The machine is connected to an electric outlet and the recorder pen filled with ink. The switch is then brought into position "diastolic" and within a few seconds the machine climbs to the diastolic pressure and remains there and follows it continuously. If a systolic reading is desired, the switch is then thrown over into the "systolic" position. The machine climbs to the systolic level and stays there continuously. When the examination is finished, the switch is brought back into the "off" position and the cuff empties automatically through the rapid deflation valve.

Measurements are carried out as follows:

Diastolic Blood Pressure. The electric switch is brought into the position "diastolic," thereby keeping the valve open as long as no sufficiently steep impulses hit the bolometer. The pressure in the cuffs and in the bolometer chamber climbs to the point at which the first sufficiently steep oscillation occurs. At this moment the valve closes and the pressure decreases. Because of the time lag, the valve is kept closed for two seconds, during which the pressure in the system falls, owing to the continuous leak. If no other impulse of the steepness for which the instrument has been set hits the bolometer in the meantime, the valve will open again after two seconds and permit compressed gas to reënter the bag-chamber system. The size of the spikes resulting from this type of operation is determined by four factors: the time lag (t_l); speed of inflation (p_a); speed of deflation (p_d); and finally, to a certain extent, by the pulse rate (t_p) (figure 3).

Systolic Blood Pressure. The switch is thrown from the diastolic to the systolic position, which means that now every puff on the bolometer opens the valve. Since in the region between systolic and diastolic pressure every pulse causes a puff, the valve is immediately opened and is kept open because of the time lag which bridges from one pulse to the next, unless the time interval from one impulse to the next is longer than two seconds. When

the pressure in the upper cuff has risen to a level just above the systolic pressure, no impulse can occur in the lower cuff, and after the time lag of two seconds, the valve closes. Air escapes through the leak until the first oscillation in the lower cuff recurs and causes the whole process to be repeated. The size of the spikes depends on the factors mentioned for the diastolic blood pressure.

The time lag of two seconds was chosen for reasons mentioned above. An inflation speed of 3 mm. Hg per second and a deflation speed of 3 mm. Hg per second were selected in order to comply as nearly as advisable with the recommendations of the American Heart Association for standardization of blood pressure readings. The size of a spike, for the diastolic as well as for the systolic pressure, caused by one single puff upon the bolometer, must therefore theoretically be 6 mm. Hg. From the manner of action described above, it is clear that the reading for the diastolic pressure is represented by the upper turning point of the diastolic spike, whereas the systolic pressure is represented by the lowest turning point of the systolic spike.

The rapidity with which readings are automatically taken by the machine can easily be deduced mathematically. After the first impulse has reached the bolometer, the time lag keeps the valve open for two seconds, during which the pressure increases 6 mm. After two seconds, the valve closes; the pressure has to fall for two more seconds in order to come back to the original level, where again a puff hits the bolometer. This means that every four seconds a reading is taken, or 15 readings per minute. If, in the meantime, the blood pressure has increased, the next reading will be taken by the machine after an interval of less than four seconds. If the blood pressure has decreased, the time interval will be longer than four seconds, depending on the amount of decrease.

It must be kept in mind that the compensation method in itself has an inherent error as demonstrated in figure 3. The descending or ascending pressure in the cuff does not always hit the pulse wave on its tip. This error depends on the speed of inflation and deflation and the pulse rate. The higher the inflation and deflation speed, the greater the error. The higher the pulse rate, the smaller the possible error. With the data standards chosen for the instrument, the maximal error at a pulse rate of 60 is 3 mm. Hg. An absolutely even blood pressure can, therefore, be recorded by an uneven tracing with maximal distortions of 3 mm. Hg. The same error can always distort the results of pressure measurements taken in the usual way, a factor important in making comparative readings.

Since the machine is limited in its inflation and deflation speed by choosing certain sizes of the inlet and outlet orifices, it is obvious that it cannot follow minute blood pressure changes which occur with a higher rapidity than the speed given by the inflation and deflation orifices. Hereby the regulation spikes gain the importance of indicating whether or not variations in blood pressure are followed by the machine minutely. If an ascending or descending branch of a tracing does not contain a spike at least every

two seconds, it means that the tracing is not as steep as the change in blood pressure and the machine is too inert to follow the original change with sufficient speed.

In order to prove that the machine in itself does not change its sensitivity, a container of about 1000 c.c. size was connected with one opening by a narrow orifice to the slit above the exposed coil of the bolometer. Another opening of the container was connected to the solenoid valve. The switch was then brought into the position "diastolic" and a tracing was obtained. The compressed gas entered through the open valve into the container,

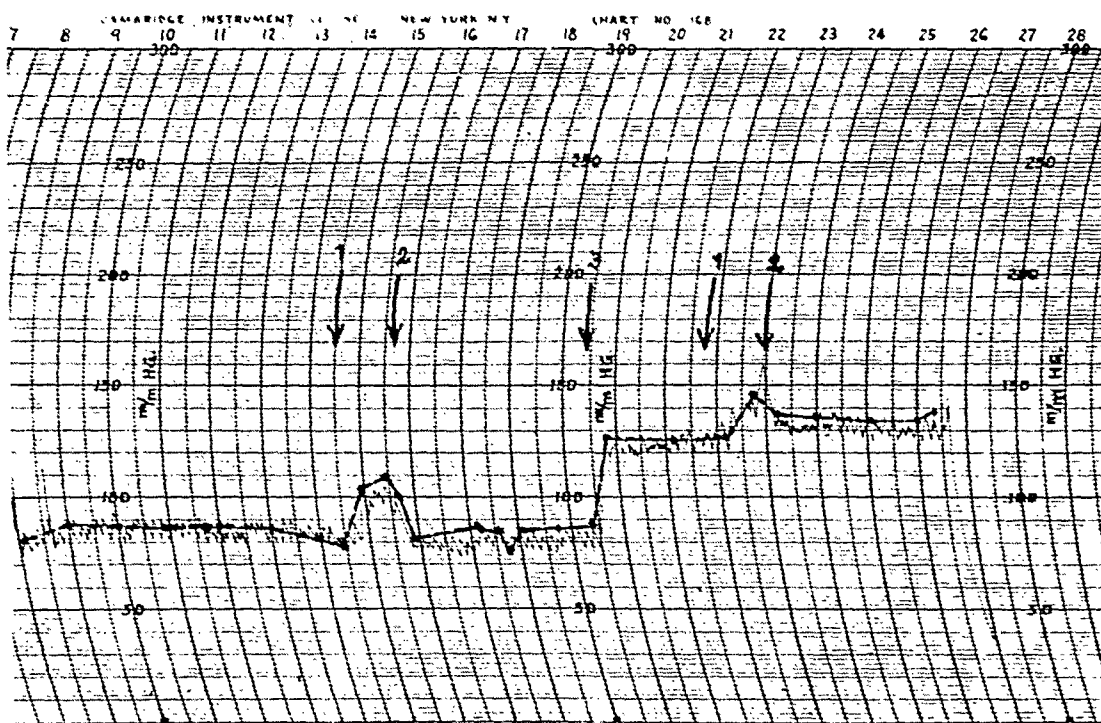


FIG. 4. Tracing of the diastolic and systolic pressure taken on both arms of a patient at the same time with two machines. Both records are later traced one over the other. At 1, a breath holding test is performed and ended at 2. At 3, the machine is switched from diastolic to systolic.

raising its pressure to a point where the speed of air directed against the bolometer was large enough to cause an impulse over the relays and to close the valve. The leak in the system now allowed the pressure to decrease for two seconds due to the time lag. After this time lag of two seconds was over, the valve reopened and the action began again. If the machine did not show any change in sensitivity, all the top points of the tracing must be at exactly the same level, while the spikes must be absolutely alike.

The diastolic adjustment was set to correspond with the values obtained by the auscultatory method. If the assumption was correct that there is a

definite characteristic change in steepness of the oscillogram at the point at which the auscultatory signs for the diastolic pressure appear, it should be possible to set the diastolic sensitivity in one case in accordance with the auscultatory finding, and this value should be correct in all other cases as well. As shown below, through comparative readings in a great number of patients, this was the case. At the same time, auscultatory controls for the diastolic pressure in one case with fluctuating blood pressure must correspond to the respective points in the sphygmotonogram. This, too, is true.

Since this sensitivity is electrically defined, we were able to create an adjustment device for the diastolic sensitivity based on electric and air flow conditions only. It is no longer necessary to adjust the machine to the patient, but the following data represent the sensitivity necessary to obtain good conformity. Air under a pressure of 50 mm. Hg, blown through a very narrow orifice of an exactly determined size against the exposed coil of the bolometer, must cause a current of 455 microamperes to flow to the relay. Since the relay itself is previously set exactly to "make" at a certain current, the diastolic sensitivity is electrically defined. If this definition is correct, one machine must not only give satisfactory conformity with an auscultatory reading in a great number of patients, but two machines attached to both arms of a patient with an equal pressure on both arms must give the same results and must show the same picture for fluctuations of the diastolic pressure. This is the case as shown in figure 4 in which the sphygmotonogram of two machines, used on the same patient, are traced, one over the other, and show a satisfactory identity.

II

It is obvious that there are certain physiological objections to the method itself. Taking long tracings of the systolic blood pressure causes a partial arrest of circulation in the arm, which is said to have detrimental effects on the nerve trunk, on the vessels, or on the muscles. After all, it must be remembered that no total arrest of the circulation takes place, since about every third pulse goes through. Thomas Lewis²⁰ in his book on "Vascular Disorders of the Limbs" proves that even total arrest in an arm up to half an hour does not cause any injury to the limb. From the many thousands of cases treated with Bier's hyperemia, it is known that even much longer periods of a high grade stagnation and pressure on the nerve trunk do not result in damage. The shortest period reported for a Volkmann contracture was five hours of total arrest *and* direct injury to the artery. We have so far examined more than 400 cases taking continuous systolic tracings for at least 10 minutes, but not more than 30 minutes without interruption. In none of these cases has any injury been observed, although some cases were examined for a period lasting from five to seven hours, records being taken for 20 minutes and the cuffs emptied for five minutes. After a period of about 10 minutes, numbness and a certain tickling sensation appear in the

fingers, which some patients call very uncomfortable, whereas others are not much disturbed by it. It is obvious that during anesthesia these questions are of no importance. In three of our cases we were compelled to stop the examination after a couple of minutes, since petechial bleeding appeared on the skin of the arm. These three patients had recovered from an infectious disease a short time before the test and had a positive Rumphe-Leede phenomenon.

Another objection concerns the influence of the discomfort on the blood pressure itself. In order to test this, tracings of 15 minutes' duration in 10 unselected patients in a quiet ward were taken, so that no other psychic influence disturbed our patients. In none of them did the systolic blood pressure change more than ± 5 mm. Hg during the whole period of observation.

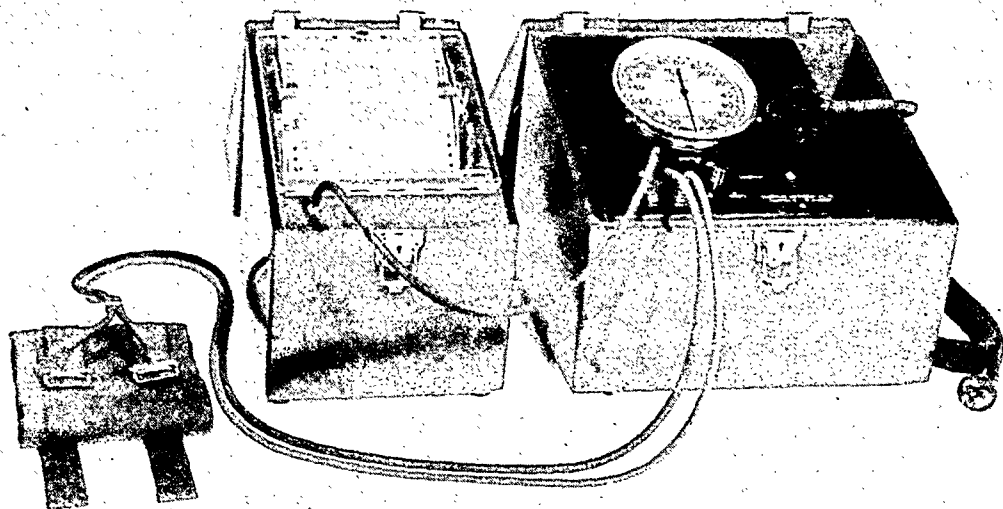


FIG. 5. The sphygmotonomograph.

Another objection involves the question whether the stagnation of blood in one part of the circulatory system decreases the circulating blood volume so much that this in itself causes changes of the blood pressure. In none of the above-mentioned 10 patients did the systolic blood pressure taken by the auscultatory method immediately before the start of the sphygmotonomogram vary more than ± 3 mm. Hg from the average blood pressure obtained during the 15 minutes of continuous recording.

In order to prove the accuracy of the device, 110 unselected male and female cases from the wards were examined in the following way:

All patients were resting in bed. The cuff of the machine (figure 5) was then applied high up and snugly on the upper arm of the patient and rapidly inflated through the special valve. The machine was then switched out and with a stethoscope a systolic and diastolic reading was taken in the usual manner. After the pressure of the cuff had come down to zero, a

diastolic and then a systolic reading was recorded by the machine, always taking the average of the second, third and fourth readings of the machine as the final result. Immediately thereafter another auscultatory reading, using the first mentioned technic, was made. The average results of the first and the second auscultatory reading were taken as a final auscultatory result. The auscultatory readings were made by the author with few exceptions, in which they were taken by other physicians. As criterion for the diastolic pressure, the end of the fourth phase was considered to be correct, a point to which the automatic diastolic recording of the machine was also adjusted.

Taking the average of 109 cases, the automatically recorded results for the systolic pressure were 0.06 mm. Hg higher than the auscultatory values found. In one case with a severe Moenckeberg sclerosis, neither the sphygmotonograph nor the auscultatory method gave a good result. In table 1 the number of cases with the different degrees of deviation are shown.

TABLE I
Deviations of Measurements Taken With the Sphygmotonograph from the Values Found by Auscultation

mm. Hg	Number of Cases			
	Systolic		Diastolic	
0	33		20	
	Minus	Plus	Minus	Plus
1-3	42	20	27	27
4-6	7	2	13	2
7-10		2		5
more than 10	2			3

For the diastolic pressure, the automatically recorded results taken from the average of 98 cases were 4.0 mm. Hg lower than the values found by auscultation. Table 1 shows the different degrees of deviation and the number of cases concerned. In 11 cases no satisfactory auscultatory readings could be obtained, and seven patients examined with the machine did not yield a satisfactory result.

In order to prove the accuracy of the machine, a microphone was placed over the brachial artery while the cuff of the machine was applied proximally. The power relay was then disconnected from the valve and connected in such a way as to close a small current through the string of an electrocardiograph when the relay pulled in. At the same time the microphone was connected to the sound recording unit of the same electrocardiograph. If the results of the sphygmotonograph are correct, the first closing

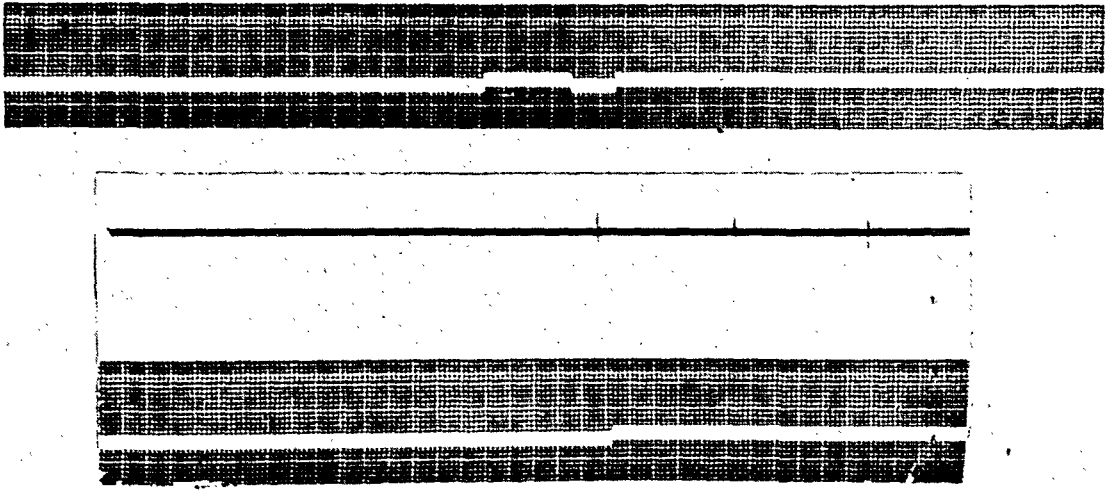


FIG. 6. Record confirming the accuracy of the measurements taken with the sphygmotonomograph. The upper tracing is taken at the systolic level, the lower at the diastolic level. A microphone is placed over the brachial artery distal from the cuff of the sphygmotonomograph. The contacts of the power relay close a current through the string of the electrocardiograph when the former is pulled in. The first sound in the systolic tracing as well as in the diastolic coincides with the first action of the machine.

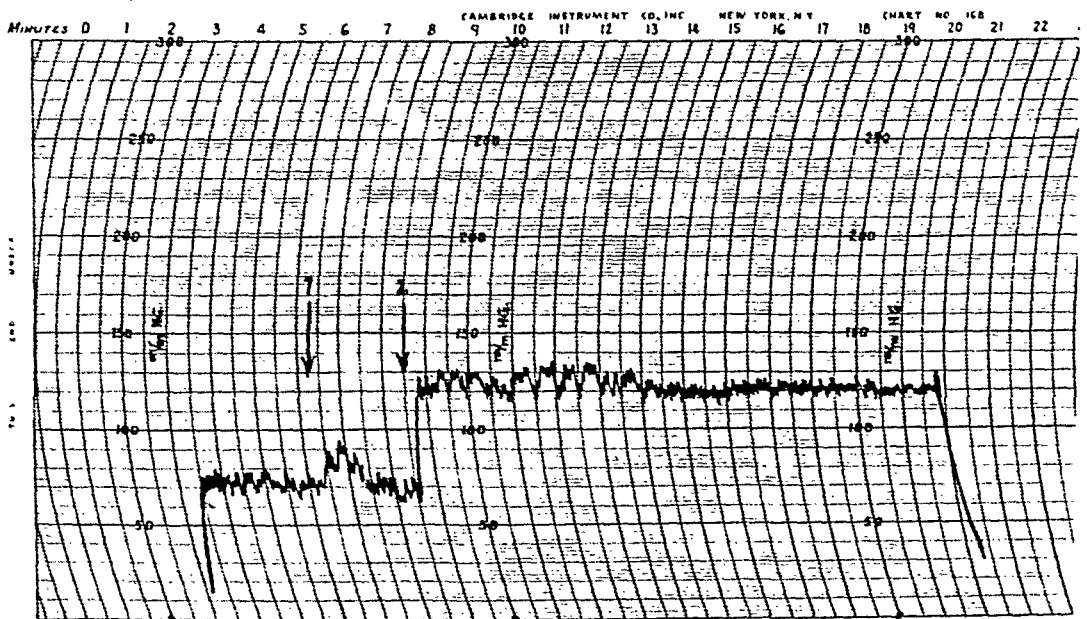


FIG. 7. V. D., white male, aged 21. Tracing of the diastolic and systolic pressure showing Mayer-Traube-Hering waves in the systolic tracing which disappear under the influence of 0.02 gram morphine. At 1 injection of 0.02 morphine. At 2 the machine is switched from diastolic to systolic.

of the circuit over the galvanometer string should coincide with the first appearance of a sound, for the systolic with falling pressure as well as for the diastolic with rising pressure. Seven patients were examined in this way. In three of them no satisfactory sound tracings could be obtained owing to faintness of the sound, involuntary movements or generally unclear sound picture. In four patients the results were satisfactory. None of them showed a deviation of more than one beat between the stethogram and the sphygmotonogram. Such a tracing is shown in figure 6.

A discussion of the question of whether the sphygmotonographic results coincide with values found by intra-arterial measurements is purposely

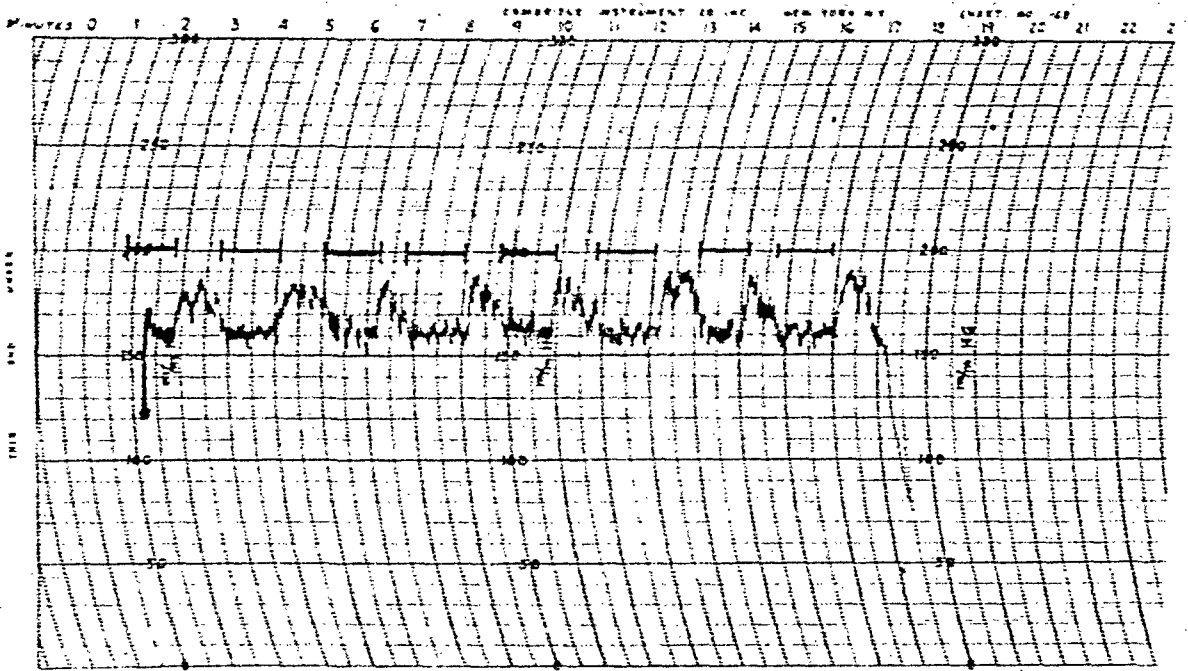


FIG. 8. L. H., white male, aged 68. The influence of Cheyne-Stokes breathing on the systolic blood pressure. The heavy lines above the tracing represent the periods of apnea, the pauses the periods of breathing.

avoided. Such comparative examinations are in the course of completion and will be reported later. The sphygmotonograph is set to give continuous readings of systolic and diastolic values as found with the auscultatory method when used accurately. This method gives the end pressure and not the side pressure, since it is an occlusive one.

A few basic facts found in most of the tracings seem worth mentioning at this point. In many persons the blood pressure does not run evenly. In many patients examined, we found Mayer-Traube-Hering waves between 15 and 30 seconds long and between 4 and 12 mm. Hg in height. These waves, as shown in figure 7, seem largely influenced by psychic emotions and very often disappear under ordinary doses of morphine. When they disappear during anesthesia, it points to the fact that the anesthesia is unduly deep, causing loss of normal circulatory reactions. They

seem to be lost in patients with excessive hypertension and to disappear in shock. They seem to be more pronounced when there is a slight increase of carbon dioxide in the arterial blood when breathing is impaired as, for example, in laryngospasm. Stress must be put upon the fact that even very

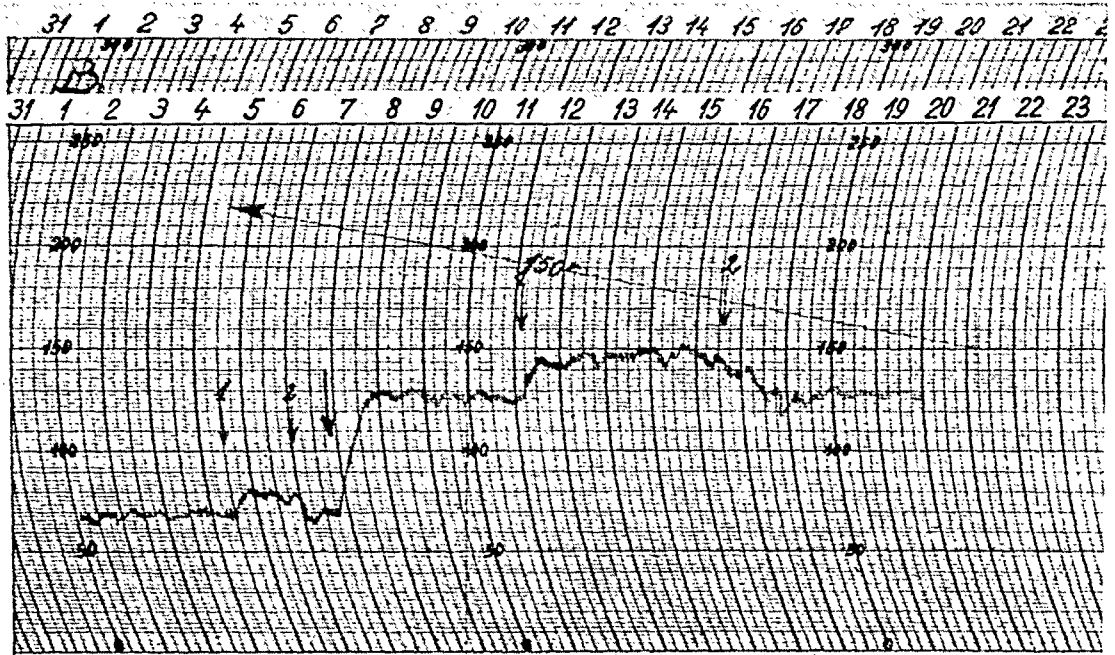


FIG. 9. A. K., white male, aged 22. The influence of a conversation on the diastolic and systolic blood pressure of a thyreotoxic man. Conversation begins at 1 and ends at 2.

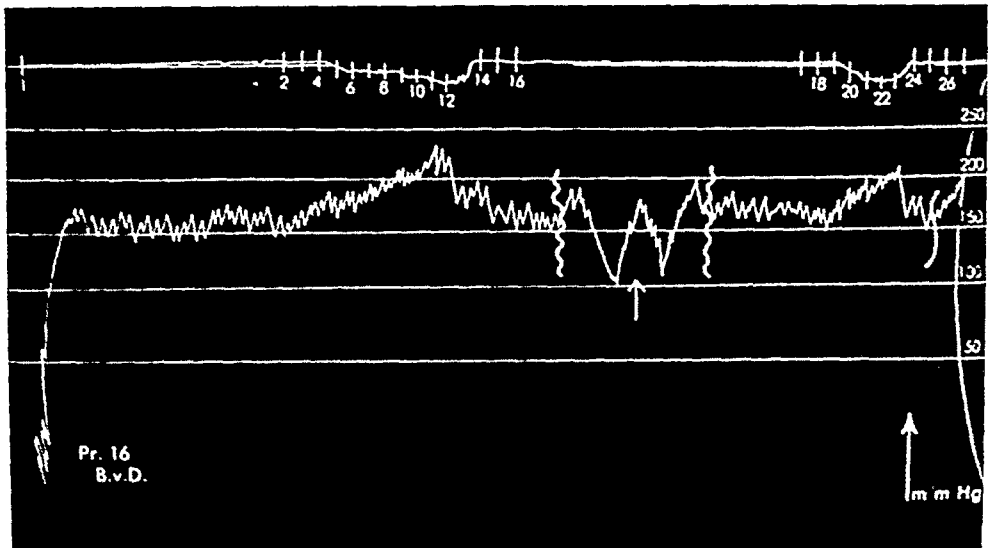


FIG. 10. Systolic blood pressure of a pilot in an airplane during a tail spin with increasing centrifugal acceleration up to 4.5 g (From H. v. Diringshofen¹²). The degree of acceleration is shown by the deviation from the horizontal of the upper marker line. (Marks 10 seconds.)

slight excitement can cause considerable increase in blood pressure; mere conversation or watching the blood pressure machine can cause increases up to 15 mm. Hg in normal persons. Such increases are much more outspoken in thyreotoxic patients and in patients with slight hypertension and suggest, when present in patients with otherwise normal blood pressure, a tendency towards hypertension.

In general it can be said that to obtain basic blood pressure conditions as represented by a steady non-fluctuating sphygmotonogram, it is necessary to have the patient at absolute rest with no disturbances whatsoever (figure 9).

We believe that this instrument in its various applications as shown in figures 8 and 10 can essentially clarify many conditions now obscure, and prevent unpleasant incidents during anesthesia.

SUMMARY

1. A machine is described which automatically takes continuous records of the systolic as well as diastolic blood pressure of man.

The principle and the detailed construction are shown and the mechanical arrangements and working conditions discussed. The inertia of the machine is shown and the meaning of the obtained tracings is discussed.

2. A simple mechanical contact device is not satisfactory for registering the diastolic pressure, since it is dependent on the magnitude of the oscillations instead of on the steepness of the ascending branch. A heated wire system (bolometer) is used to transform the puffs of air into electric currents.

3. The steepness of the ascending branch of the diastolic oscillation is an exact criterion for the diastolic pressure.

4. The accuracy of the sphygmotonograph was proved by comparisons with the auscultatory method in 109 patients. The average difference for the systolic pressure was 0.06 mm. Hg, for the diastolic pressure 4.0 mm. Hg.

5. Records taken from both arms of the same patient with two machines are identical.

6. Taking uninterrupted records for a period of 30 minutes with partial arrest of the circulation in the limb concerned does not produce any detrimental effect on the vessels, nerves or muscles.

7. The partial arrest of circulation and the pressure on the limb do not produce changes in the blood pressure.

8. Comparative measurements with the Korotkov method, using a recording microphone instead of the stethoscope, show the accuracy of the sphygmotonograph.

9. Many normal persons show Mayer-Traube-Hering waves of a wave length of about 30 seconds and a height up to 12 mm. Hg in size under excitement and impaired breathing conditions.

10. Even slight mental work or excitement may cause a considerable in-

crease in diastolic and systolic blood pressure, especially in individuals in the very beginning of hypertension.

I wish to express my thanks to the engineering staff of the Cambridge Instrument Co. for their assistance in planning many technical details.

REFERENCES

1. BRANOWER, W.: Anesthesia complications and their management, *Surg. Clin. North Am.*, 1937, xvii, 83-92.
- NEFF, W.: Graphic recording of pulse and respiration during anesthesia, *Anesth. and Analg.*, 1939, xviii, 342-348.
2. KIRSCHNER, M.: Wesentliche Probleme der Chirurgie, *Deutsch. med. Wchnschr.*, 1928, liv, 1541-1544.
3. DARROW, C. W.: Continuous records of systolic and diastolic blood pressure, *Arch. Neurol. and Psychiat.*, 1937, xxxviii, 365-370.
4. KRONFELD, A., MÜELLER, A., and REINER, R. C.: Untersuchungen mit dem Autotonographen, *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1933, cxlv, 62-98.
5. LANGE, K.: Die fortlaufende selbsttätige Messung und Registrierung des menschlichen Blutdrucks, *Deutsch. med. Wchnschr.*, 1932, lviii, 406-407.
- LANGE, K.: Methoden und Ergebnisse der fortlaufenden selbsttätigen Blutdruckmessung beim Menschen (Autotonographie), *Verhandl. d. deutsch. Gesellsch. f. Kreislauforschung*, 1932, 60-68.
- LANGE, K.: A machine for the continuous recording of systolic and diastolic blood pressure in man, *Bull. New York Med. Coll., Flower and Fifth Avenue Hospitals*, 1941, Vol. 4, No. 2.
6. HESSE, H.: Autotonograph und fortlaufende Blutdruckmessung, *Ztschr. f. Kreislauforsch.*, 1935, xxvii, 473-491.
7. KOLLS, A. C.: Continuous blood pressure tracings in man, *Jr. Pharmacol. and Exper. Therap.*, 1920, xv, 433-441.
8. KOCH, E., and SIMON, H.: Ein neues Verfahren zur fortlaufenden Verzeichnung des Blutdrucks am Menschen, *Ztschr. f. d. ges. exper. Med.*, 1929, lxxv, 594-603.
9. OMBERG, A. C.: Apparatus for recording systolic blood pressure, *Rev. Scient. Instruments*, 1936, vii, 33-34.
10. STOKVIS, B.: Uninterrupted, automatic, bloodless registration of blood pressure in man, *Nederl. Tijdschr. v. Geneesk.*, 1937, lxxxix, 1805-1811.
11. DOUPE, I., NEWMAN, H. W., and WILKINS, R. W.: Method for continuous recording of systolic arterial pressure in man. I. *Physiology*, 1939, xcv, 239-243.
12. v. DIRINGSHOFEN, H.: Die Wirkung von gradlinigen Beschleunigungen und von Zentrifugalkräften auf den Menschen, *Ztschr. f. Biol.*, 1934, xcv, 559-566.
13. POECK, E.: Das Verhalten des Blutdrucks bei Evipanarkosen, *Chirurg.*, 1933, v, 456-459.
14. GROEDEL, F. M., and McCLELLAN, W. S.: Fortlaufende Blutdruckkontrolle während des Bades, *Ztschr. f. d. ges. phys. Therap.*, 1933, xlv, 211-215.
15. PEEMOELLER, F., and LUND, O.: Über Bäderwirkungen, *Arch. f. exper. Path. u. Pharmakol.*, 1935, clxxviii, 86-100.
16. REINER, R. C.: Psychologische Untersuchungen mit dem Autotonographen, *Med. Welt*, 1936, 10, 811-816.
17. FASSHAUER, W., and OETTEL, H. I.: Klinischer Beitrag zur Veränderung der vasomotorischen Selbstregulation, *Klin. Wchnschr.*, 1938, xvii, 620-622.
18. v. BERGMANN, G.: *Funktionelle Pathologie*, 1932, Julius Springer, Berlin.
19. BAZETT, H. C., LAPLACE, L. B., and SCOTT, I. C.: Pressure changes induced in the vascular system as result of compression of limb and their effect on indirect measurements of lateral pressures, *Am. Jr. Physiol.*, 1935, cxii, 182-201.
20. LEWIS, SIR THOMAS: *Vascular disorders of the limbs*, 1936, Macmillan, New York City.

CASE REPORTS

LARYNGEAL AND SYSTEMIC HISTOPLASMOSIS (DARLING) *

By PAUL A. VAN PERNIS, M.D.,† MIRIAM E. BENSON, S.B., and
PAUL H. HOLINGER, M.D., *Chicago, Illinois*

MEDICAL interest in histoplasmosis (Darling) has been aroused recently by the increased number of reports published. These accounts indicate that this endemic disease has become more prevalent or that it has existed unrecognized. The difficulties encountered in clinical diagnosis of the disease are due apparently to the variety of symptoms presented by these patients. The specific organism has been isolated by cultures in only a few patients during life or from tissues post mortem. There is no information concerning the morbidity of the disease because all patients known to have had the infection have died. Little is known about the predisposing factors of the infection. Heredity and environment seem to have no effect on the course. The disease, though endemic, is not restricted in geographic distribution. Twenty-two males and 10 females have died; their age incidence ranges from six months to 69 years. The course of the disease seems to be short in the very young and longer in older persons and is unaffected by climate, season, or state of hygiene. Occupation seems not to be a factor, although many of the patients lived in rural districts or had close contact with farm products.

The causal organism is *Histoplasma capsulatum*, a member of the fungi imperfecti. It exists in yeast and mycelial forms. The yeast form is pathogenic in man although the mycelial form was found once in human tissues.¹ The hyphae are 2.5 to 11.5 μ in diameter and may be either straight, branched, or septate. Chlamydospores range from 4 to 10 μ in diameter and are rich in fat. They are sessile, lateral, intercalary, or pedicellate. The characteristic ascus-like bodies are 10 to 25 μ in diameter, rich in fat, and must be present for identification of the fungus organism. At first they are smooth or crenate but become spinose with barbs as long as 5 to 6 μ . They are attached to hyphae terminally, laterally, or in the interstices.² The fungus grows well on various media and the disease can be reproduced in animals. The mode of infection, distribution outside the body, and the nature of immunity, if any, are unknown.

The organism, once established in the body, invades many tissues. There has been enlargement of the liver or spleen with or without tubercle-like nodules in most of the cases; small, hemorrhagic, firm, white nodules or patchy consolidation of the lungs in 50 per cent; focal necrosis in cervical, axillary, tracheo-bronchial, mesenteric and periaortic lymph nodes in many; necrosis, hemorrhage

* Received for publication August 25, 1941.

From the Henry Baird Favill Laboratory and the Department of Peroral Endoscopy of St. Luke's Hospital, Chicago, Illinois.

† The John Jay Borland Fellow in Clinical Research.

or enlargement of the suprarenal glands in 10; multiple ulcerations, scaling, nodular thickenings, or purpuric spots in the skin of six; granulomatous lesions of the epiglottis, vocal cords, and larynx in two; small gray nodules on the serosa of the duodenum, ileum and colon; granular annular ulcers of the jejunum, ileum, and colon; longitudinal ulcers of the colon and rectum; small gray nodules on the anterior surface of the left ventricle of the heart, meninges, thymus, and pancreas; and small hemorrhages in the kidney.

Microscopic findings vary as widely as the gross pathological changes. Coccoid bodies corresponding to the yeast form of *Histoplasma capsulatum* have been described in alveolar cells; in monocytic phagocytes of alveolar and bronchial exudates, nasal, buccal, palatine, or laryngeal ulcers, skin, epicardium, meninges, duodenal serosa, intestinal lamina propria, periportal regions of the liver, necrotic regions in the spleen, lymph nodes, renal medulla and glomerular tufts, sternal bone marrow and ear exudates; in endothelial cells of the capillaries, liver, spleen, lymph nodes, and skin; in medullary and cortical cells of the suprarenal gland; in the epithelium of the skin; and in the acinar epithelium of the prostate.

Accompanying these parasitized cells are lymphocytic exudates with or without necrosis, scar tissue, or hyaline masses. Giant cells were reported once in the spleen. The lesions resemble tuberculosis. Watson³ stated that the first change following parasitism of the cells is necrosis and lymphocytic exudates, followed by scarring and hyalinization. In ulcers, lymphocytes are numerous, and there are very few polynuclear leukocytes. Phagocytized mononuclear cells are abundant. In the lung a lymphocytic bronchopneumonia may develop. The mycelial form of the organism has been seen in the bronchial exudate of one patient.¹

The invaded cells may have only four or five coccoid bodies or 50 or more. These bodies are 2 to 4 μ in diameter with central dark blue granules and pale pink cytoplasm, in hematoxylin and eosin-stained preparations. A narrow refractile zone surrounds the cell. The granules may be single or five to six in number. They sometimes form chains or crescents within the organism that suggest the merozoites of protozoan parasites. At times the cytoplasm appears vacuolated.

Darling⁴ listed the syndrome of anemia, fever, splenomegaly, and weight loss as characteristic of the disease. Symptoms referable to the respiratory tract were cough, rhinitis, rhinorrhea, sore throat, hoarseness, and dyspnea. Gastrointestinal symptoms were sore gums, ulcers of the mouth or tongue, nausea, emesis, epigastric fullness, diarrhea with or without blood, and loss of weight. The liver, spleen, or lymph nodes may or may not be enlarged. Low-grade fever reported in many patients markedly simulates the afternoon or early evening fever of tuberculosis. Blood conditions vary. Five cases had a chronic otitis media. Ulcers, purpura, bullae, scaling, jaundice and brown pigmentation of the skin have been described.

Various agents have been tried in an attempt to halt the progress of the disease. Among them are quinine, potassium iodide, neoarsphenamine, bismuth subnitrate, stovarsol, ionized copper, roentgen-ray, splenectomy, sulfanilamide, pentnucleotide, blood transfusions, potassium arsenite and tartar emetic. Meloney⁵ suggested the use of antimony and potassium compounds.

Only fatal infections thus far have been recorded. Some patients seem to die from a pneumonia, others from "heart failure." Lesions of the suprarenal glands have been reported in 10; death in these may have been due to suprarenal insufficiency.

Histoplasmosis may be diagnosed in various ways. Stains of the peripheral blood and of bone marrow biopsies may afford a clue. Biopsies of available tissues, such as laryngeal, buccal, or rectal ulcers, may furnish histological and cultural evidence of the condition. Dextrose broth culture filtrates of the fungus isolated from lesions produce specific immediate and delayed skin reactions.⁸ An immediate reaction, like an urticarial wheal 1 to 1.5 cm. in diameter, appears with undiluted filtrate in 15 to 30 minutes after the injection. The delayed reaction, clearly visible after 18 to 24 hours, consists of a marked erythema and swelling of the skin which gradually disappears after five or six days. Dextrose broth filtrates treated with three volumes of acetone yield the specific substance responsible for the skin reaction. This flocculent precipitate, when redissolved in saline and injected intradermally, produces a typical erythematous wheal in 30 to 60 minutes.

CASE REPORT

A 63-year-old Latvian bartender had an irritation of his throat and increasing hoarseness for 18 months. He had lost 40 pounds in weight in six months and for one month had difficulty in swallowing. He noticed increasing weakness and a chronic cough, productive of a thin, watery sputum. His appetite was poor, and he had a sensation of epigastric fullness aggravated by food but relieved by emesis, soda and warm water. He had impaired hearing in his left ear since childhood, associated with an occasional thick yellow exudate. In 1915, he had diphtheria; in 1932, pleurisy. Syphilis and gonorrhea, contracted in 1925, had been adequately treated.

On admission to the hospital the patient appeared to have lost weight. His blood pressure was 115 mm. Hg systolic and 75 mm. diastolic, pulse 80, and temperature 98.6° F. The lips and buccal mucosa were pale. The gums were soft and had receded. Hearing in his left ear was markedly impaired. The chest was emphysematous and the lungs hyperresonant but without adventitious sounds. The abdomen was protuberant and the liver palpable three fingers' breadth below the costal margin. There was wasting of the muscles of the extremities and coarse thickening and longitudinal ridging of the finger and toe nails. Mirror examination of the larynx revealed a small polypoid tumor in the midportion of the phonating edge of the left true cord. The aryepiglottic folds and arytenoids were thickened and their laryngeal surfaces had a soft, slightly ulcerated mass extending across the entire posterior commissure. The lesion was red and covered with a gray exudate. The motility of the cords was impaired. Physical examination was otherwise normal. The Kahn test was negative, the urine was normal, and repeated stool and sputum examinations were negative. Sternal biopsies and differential blood stains were normal. The red blood cells ranged between 5,120,000 on admission to 4,680,000 shortly before death; the hemoglobin was 15.4 to 12.8 grams per cent, and the leukocytes 7,950 to 5,620 per cu. mm. Roentgen examination of the larynx suggested an irregularity of the body of the thyroid cartilage and a slight increase in density about the arytenoids. The lungs had increased hilar shadows and calcified nodules in the left hilum, and the peribronchial markings were increased. A gastrointestinal study demonstrated only a decreased motility of the ileum. The liver and spleen were enlarged. Direct examination of the larynx substantiated the findings of mirror examination. A verrucous mass extended across the posterior commissure, spread

laterally into the ventricles and superiorly to involve the posterior portions of the false cords. The polyp on the left true cord as well as tissue from the posterior commissure was removed. The tissues were diagnosed as histoplasmosis of the larynx by Dr. Edwin F. Hirsch. Other tissues were removed two weeks later for further histological study and bacteriological culture. *Histoplasma capsulatum* was isolated from them on various mediums. The patient was discharged from the hospital and, until his last admission two months later, lost 80 pounds in weight, became progressively weaker, and developed a bronze pigmentation of the skin. As nutrition seemed of prime importance, treatment was so directed. Small ulcers appeared in the

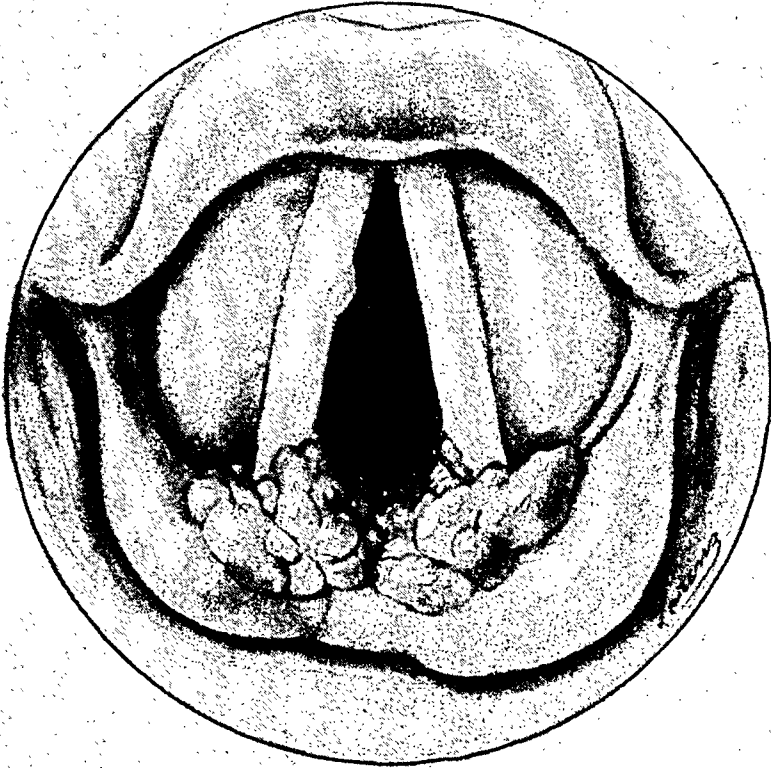


FIG. 1. Drawing illustrating the location and extent of the histoplasma granulation tissue lesions of the larynx.

left premolar region and on the right side of the base of the tongue from which no unusual organisms were cultured. He had late afternoon or early evening rises in temperature to 100° F. The constituents of the blood were within normal ranges. Neoarsphenamine, sulfanilamide, potassium iodide, yellow bone marrow and potassium permanganate gargles did not improve his general condition. The ulcers of the mouth and tongue healed. The laryngeal lesion improved. During one month he received 280 grains of tartar emetic intravenously and by mouth, but without improvement generally. The patient died approximately five months after the diagnosis of histoplasmosis had been made.

Autopsy was done eight hours after death. The body weighed 100 pounds. There was poor oral hygiene with a blue-black discoloration of the gingival margins and caries of the teeth. The skin was generally pigmented light brown. Emaciation

was marked. The toe and finger nails were thickened and had prominent longitudinal ridges. The axillary, periaortic, abdominal, tracheobronchial, cervical, inguinal and biliary lymph nodes were not enlarged but the centers of some were yellow and slightly soft. Along the root of the mesentery were small, glistening, white nodules not larger than 3 mm. in diameter. Dense fibrous adhesions were between the lateral chest wall and the right lung. There was a moderate atherosclerosis of the aorta. The esophagus had slight epitheliosis and a small diverticulum. The heart had only a moderate cloudy swelling. It weighed 250 grams. The right suprarenal gland weighed 14.2 grams, had a firm fibrous capsule, and its center was caseous, gray-yellow

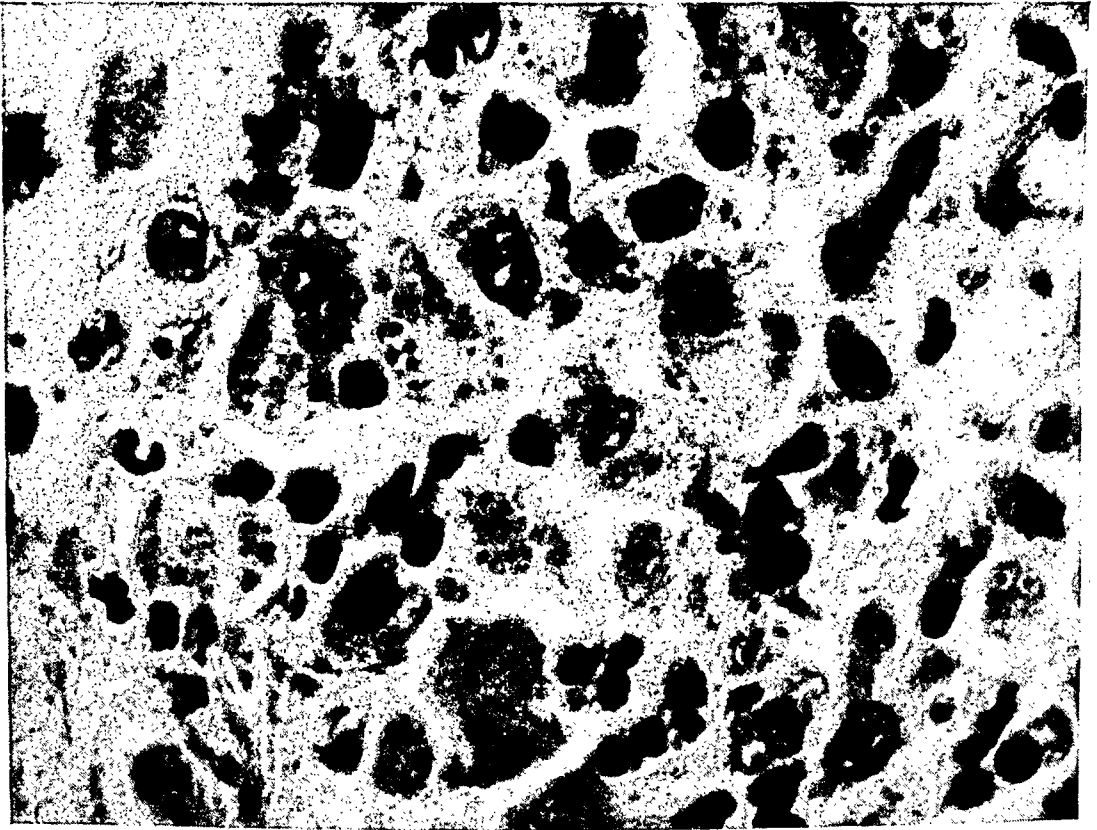


FIG. 2. Photomicrograph illustrating the large phagocytes with the histoplasma inclusions in the laryngeal granulation tissues. Hematoxylin-eosin stain $\times 980$.

tissue. The similar left suprarenal gland weighed 14.5 grams. No normal suprarenal tissue remained. Each kidney weighed 200 grams and had slight senile nephrosclerosis. There were no changes of the gall-bladder and bile ducts, pancreas and pancreatic ducts. The pancreas weighed 86 grams. The liver had a moderate chronic passive hyperemia and weighed 1890 grams. The spleen weighed 475 grams and had only scattered gray-white nodules 2 to 4 mm. in diameter. The left lung weighed 595 grams; the right, 900 grams. They had only fibrous adhesions covering the pleura of the right lung. The stomach, duodenum, ileum, colon, and rectum were normal. The mucosa of the jejunum was hyperemic. Scattered regions with blebs seemed to contain gas and were on both the mesenteric and antimesenteric sides. These ranged from 3 mm. to 3.2 cm. in diameter. The larger regions seemed multiloculated and were raised as much as 1 cm. above the surrounding mucosa.

The vocal cords and larynx were hyperemic. In the right posterior commissure was a finely granular, gray-white tissue 0.6 by 0.2 cm. with several depressions 2 to 3

mm. deep. The vocal cords were smooth. In the right pyriform sinus were five gray-white nodules, 4 mm. in diameter. Another nodule was on the right posterior pillar. The left pyriform sinus had 11 similar nodules, three of which were confluent and shaped like a clover-leaf. Three other nodules were on the left posterior pillar. The base of the tongue had similar nodules. The tonsils were atrophied. The left middle ear was fibrous and hyperemic. The surrounding bone was soft and porous. The ear drum was perforated, thick, and gray. The external canal was filled with waxy material. A circular depression, 3.8 by 3.2 cm., of the frontal bone in the midline apparently was an old injury. The calvarium, dura, brain, dural sinuses, cerebrospinal

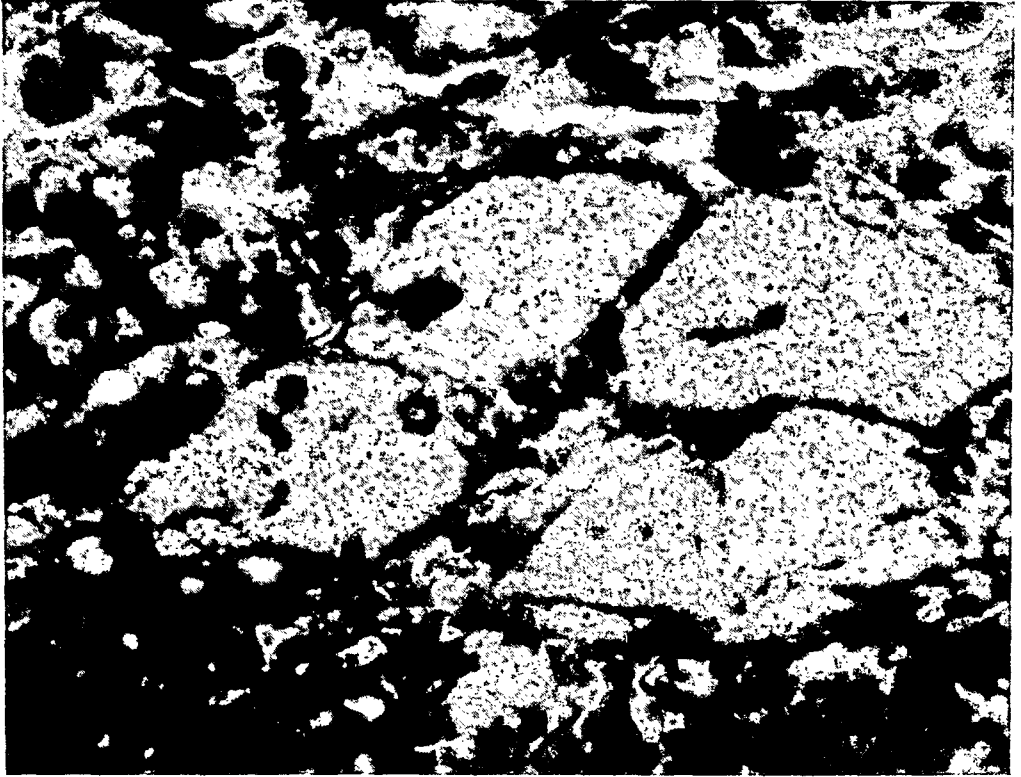


FIG. 3. Photomicrograph illustrating the parasitic invasion of swollen cortical cells of the suprarenal gland. Phosphotungstic acid-hematoxylin stain $\times 920$.

fluid, hypophysis, accessory nasal sinuses, right middle ear, right and left mastoid processes, were without change.

Cultures of heart blood, cerebrospinal fluid, right and left suprarenal glands, pericardial fluid, and left ear exudates on Endo's agar, blood agar, dextrose agar, beef heart broth and dextrose broth were overgrown by *B. mucosus capsulatus*, and continued to be when subcultured twice, a week apart. *Histoplasma capsulatum* was not recovered from these cultures after three weeks.

Lymph nodes from various places were similar in histological detail. They were moderately edematous. In the cytoplasm of monocytic macrophages were spherical refractile bodies 2 to 4 μ in diameter. In the centers of these bodies were one to five dark blue granules; outside was a clear halo. There was a thin refractile capsule. Some of these bodies were extracellular. There were many large and small fibrous scars. With high magnification the centers of these scars consisted of disintegrating nuclei of monocytic cells and many pale oval bodies 2 to 4 μ in diameter without

basophilic granules. Outside of these regions in the larger scars was a zone of lymphocytes resembling a tubercle. An occasional multinucleated giant cell was found in some of the lymph nodes. Some of the parasitized cells had one or two oval bodies; others had 30 to 50. Sections stained by the Ziehl-Neelson method revealed no acid-fast organisms. Parasitized cells were also found in the sinuses. In a few places where the capillary endothelium was thickened, a parasitized endothelial cell was seen. In phosphotungstic acid-hematoxylin preparations the granules were dark blue and the clear zone faintly orange. In eosin-methylene blue preparations the granules were bright blue and the clear zone faintly pink. In preparations stained by Masson's trichrome method, the granules were brown to black and the clear zone was faintly green. These staining reactions correspond to those of collagen. The tracheobronchial lymph nodes contained monocytic phagocytes with carbon pigment and yeast bodies in their cytoplasm.

Tissues from the left middle ear were chronic granulation tissues with many mononuclear cells filled with the characteristic oval histoplasma organisms. Bone marrow sections showed the trabecular spaces filled with lymphocytes and mononuclear cells, singly or in clumps, containing parasites 2 to 4 μ in diameter.

Extensive portions of the histological preparations of the left and right suprarenal glands were necrotic. Radiating from the fibrous capsule into the granular debris were stalks of poorly vascular chronic granulation tissue. The necrotic portions were tissue debris with polynuclear leukocytes, lymphocytes, and mononuclear phagocytes. Much of the tissue debris with high magnification consisted of disintegrating masses of yeast bodies. At one place next to the fibrous tissue capsule were a few large cortical cells in parallel rows. The cytoplasm of these cells was filled with yeast bodies. Sections stained by the Ziehl-Neelson method failed to reveal acid-fast organisms. Some of the necrotic tissues were surrounded by zones of lymphocytes and a few large multinucleated giant cells.

The tissues of the larynx had a narrow regular surface squamous epithelium. The stroma was dense fibrous tissue with small foci of lymphocytes and monocytes. There were numerous mucous glands. In the cytoplasm of these gland cells were many parasites. They were demonstrated clearly in sections stained by hematoxylin and mucicarmine. The mucin stained bright pink, the vesicular nuclei had dark blue chromatin granules and in the cytoplasm both basally and toward the lumen were dark blue bodies 2 to 4 micra in diameter surrounded by a refractile halo. These corresponded to the parasites in other sections. Tissues of the pyriform sinuses had a narrow surface squamous epithelium resting on a dense fibrous tissue stroma containing many mucous and serous gland acini. In the fibrous tissue stroma were foci of lymphocytes and monocytes with parasitized cytoplasm. The cytoplasm of the mucous secreting cells was also parasitized. This was demonstrated best by hematoxylin and mucicarmine stains.

The mucosa of the jejunum was autolyzed. After a careful search only a few mononuclear cells were found at the tips of the villi, containing a few parasites. The submucosa was separated from the lamina propria and muscularis mucosa by a clear space but otherwise the jejunum was normal. Sections of the ribs, sternum, and vertebrae had only a few monocytic cells with cytoplasm containing parasites. In the muscle tissues about a rib was an encysted trichina larva. Scattered in the red pulp and Malpighian corpuscles of the spleen were large, single, and clumped parasitized mononuclear cells. There were also small fibrous scars with many parasitized monocytic cells. The liver had a chronic passive hyperemia. The fibrous connective tissue about the portal canals was increased and had many lymphocytes and large parasitized mononuclear cells. The adjacent liver cells also were parasitized. Some of the liver cells detached from the cords and in the connective tissues had many parasites. The gallbladder, pancreas, myocardium, and kidney tissues had no unusual changes. The

pleura of the lungs was thickened by fibrous tissues. The alveoli had fibrin, red blood cells, lymphocytes, and many monocytic phagocytes containing carbon pigment, blood pigment, or parasites. A few parasitized cells were in the alveolar septa. Along the endothelial edge of the capillaries were a few clusters of swollen parasitized mononuclear cells. Bronchial exudates also contained parasitized cells and small fibrous scars had the yeast-like organisms and vacuolated multinucleated giant cells. The lymphoid tissues along the interlobular septa of the thyroid had a few parasitized mononuclear cells. These cells were found also elsewhere. The testes had no changes except a few small collections of lymphocytes and large parasitized mononuclear cells beneath the tunica albuginea. A few parasitized cells were found in the acinar epithelium and lumina of the prostate. Histological preparations of the brain, hypophysis and Gasserian ganglion were without noteworthy changes.

CULTURAL STUDIES

Tissues and exudates removed from the larynx five months before death were cultured on various media at 37° C. and at room temperature. Growth was obtained easily after three to five days. Subcultures were made many times and the organism continued to grow, predominantly in the mycelial form. Various cultural studies of this and of material obtained from animals inoculated with the initial growth have been reported.⁸

The fungus grows on decaying material of many kinds, in sunlight and in the dark. Its growth is more abundant in the dark and more so in moist material. It is a fairly resistant organism but is killed in the autoclave in one hour at 15 pounds pressure or when subjected to freezing for one-half hour. When dextrose broth cultures were treated with various chemical agents in strength up to 10 per cent, the organism was very resistant to common acids, alkalies and sulfanilamide derivatives. There was no resistance to thymol, potassium permanganate, or tartar emetic.

ANIMAL STUDIES

Fifteen white mice were injected intraperitoneally with 2 to 3 c.c. of a heavy suspension of the mycelial form of *Histoplasma capsulatum*. Two died; the rest were killed at intervals of one to six weeks. At autopsy nine had no gross pathological changes. One mouse had an abscess of the groin from which the fungus was recovered. Five mice had enlargement of the liver and spleen, but only one had minute gray nodules in the liver and spleen after three weeks. In two mice the mesenteric lymph nodes were enlarged. The fungus was recovered from either the liver, spleen, or lungs of all but four mice. Characteristic histological changes were found in the liver and spleen of all 15 and in the lungs of nine mice. Ten gave delayed positive skin reactions when 0.1 c.c. of a 1:100 dilution of dextrose broth filtrates of the fungus was injected intradermally. Five mice tested gave immediate positive reactions when 0.1 c.c. of an acetone precipitate of dextrose broth culture redissolved in saline was injected intradermally. Fifteen uninoculated mice gave negative results when tested for skin reactions.

Yeast forms of the fungus, 2 to 4 μ in diameter, were recovered from four of the mice. On subculture these changed to the mycelial form. Large yeast forms corresponding to those described by Moore⁶ were recovered from one of the mice. On subculture smaller yeast forms developed and soon changed to

the mycelial form. Other mice inoculated with these large forms showed characteristic histological findings for *H. capsulatum*. Cultures of spleen and liver of these mice produced the mycelial form with characteristic chlamydo spores.

Rats inoculated intraperitoneally with the mycelial form consistently failed to show any gross, histological, or cultural characteristics of the disease. Skin tests were negative.

Guinea pigs inoculated intraperitoneally gave variable results. No gross characteristic changes were evident. Histological evidence of the disease was found in the spleen and lymph nodes of only two guinea pigs. Positive cultures were obtained from the liver of one and the spleen of both of these guinea pigs but cultures of other animals were negative. One-tenth c.c. of a 1:10 dilution of histoplasma dextrose broth filtrate gave positive skin tests in only these two guinea pigs.

Rabbits inoculated intraperitoneally, intracerebrally, intravenously, intrapleurally and by gavage consistently gave negative gross, histological, cultural and skin test results. Eight mice, each fed 1 c.c. of a histoplasma suspension 10 times over a period of two weeks, also gave completely negative results.

DISCUSSION

So that this disease may be fully understood and a cure effected, the fact should be recognized that it simulates many other clinical syndromes, especially tuberculosis. Not only are the clinical symptoms similar to tuberculosis but also the gross and microscopic pathological changes. Our case and that of Brown, Havens and Magath⁷ had symptoms suggesting laryngeal tuberculosis or a tumor. Suprarenal insufficiency probably was the cause of death in our patient. Part of the classical syndrome of Addison's disease was present, but the blood chlorides were normal and the blood pressure was not lowered.

The remarkable feature histologically is the parasitic invasion of the cells in the suprarenal cortex. The fungus does not affect only the reticuloendothelial system but also invades epithelial cells. Similar parasitic invasion of the epithelial cells in the liver and in mucous and serous glands of the laryngeal tissues was also observed.

SUMMARY

The clinical course and postmortem findings of a patient with laryngeal histoplasmosis is described. Although the symptoms caused by the fungus infection of the larynx were the patient's chief complaint, intracellular parasitism and destruction of the suprarenal glands by the disease caused an Addison's syndrome. Intracellular involvement of liver tissues and mucus secreting glands was observed. Broth culture filtrates of the fungus isolated from laryngeal lesions produced specific immediate and delayed skin reactions in the patient and in animals experimentally infected. The specific substance responsible for the skin reactions was precipitated with acetone and was readily soluble in saline solutions.

BIBLIOGRAPHY

1. HUMPHREY, A. A.: Reticuloendothelial cytomycosis (Histoplasmosis of Darling), Arch. Int. Med., 1940, lxx, 902-918.

2. DEMONBREUN, W. A.: The dog as a natural host for *Histoplasma capsulatum*, Am. Jr. Trop. Med., 1939, xix, 565-587.
3. WATSON, C. J.: The pathology of histoplasmosis (Darling) with special reference to the origin of the phagocytic cells, Folia haematol., 1928, xxxvii, 70-93.
4. DARLING, S. T.: Histoplasmosis: A fatal infectious disease resembling Kala-Azar found among the natives of tropical America, Arch. Int. Med., 1908, ii, 107.
5. MELENEY, H. E.: Histoplasmosis (reticuloendothelial cytomycosis); A review with mention of 13 unpublished cases, Am. Jr. Trop. Med., 1940, xx, 603-616.
6. MOORE, M.: *Posadasia pyriformis* and *Posadasia capsulata*, two causative organisms of Darling's histoplasmosis in the United States, Ann. Mo. Bot. Gardens, 1934, xxi, 347.
7. BROWN, A. E., HAVENS, F. Z., and MAGATH, T. B.: Histoplasmosis: Report of a case, Proc. Staff Meet. Mayo Clin., 1940, xv, 812-816.
8. VAN PERNIS, P. A., BENSON, M. E., and HOLINGER, P. H.: Specific cutaneous reactions with histoplasmosis, Jr. Am. Med. Assoc., 1941, cxvii, 436-437.

SYPHILIS OF THE STOMACH: A CASE REPORT*

By WALTER LINCOLN PALMER, M.D., F.A.C.P., RUDOLF SCHINDLER, M.D.,
FREDERIC E. TEMPLETON, M.D., and ELEANOR M. HUMPHREYS, M.D.,
Chicago, Illinois

THE occurrence of gastric syphilis has been so well established that further proof of its existence is, in our opinion, not needed.¹⁻³¹ The instructive case herein reported is of interest because the classical pathologic criteria are so well fulfilled and because the diagnostic difficulties are well illustrated.

CASE REPORT

The patient, a male 36 years of age, was admitted to the University clinics on November 26, 1940, complaining of anorexia, bloating, distention, abdominal distress, nausea, vomiting and loss of weight. He had been perfectly well until January 1940, when he began to notice a continuing lack of appetite. On May 5 he experienced nausea and vomited food following the noon meal. This recurred for five successive days and then disappeared. Abdominal bloating, distention and discomfort persisted and were not improved by a month's vacation in July. In August a gnawing epigastric "hunger pain" appeared, coming on about 11:30 a.m., 4 p.m., and 4:30 a.m., and lasting 15 to 20 minutes unless food or soda was taken, in which case prompt and complete relief was obtained. Occasionally nausea appeared in the midafternoon and usually led to emesis unless relieved by food. In the six months prior to admission the patient had lost 25 pounds in weight. The additional history was essentially irrelevant except for the statement that at the age of 17, following coitus with an infected person, the patient had developed a "pimple" on the dorsal shaft of the penis, over which a crust had formed with healing in four weeks. Apparently syphilis had not been suspected and hence no treatment had been instituted. Physical examination in November 1940 disclosed no significant abnormality except a scar on the left dorsum of the shaft of the penis. The neurologic examination was normal. The blood Wassermann and Kahn tests were both strongly positive (four plus) on two occasions. The spinal fluid Wassermann test was negative; the cell count was 6, Pandy negative, the pressure normal, the colloidal gold curve normal. The red blood cell

* Received for publication August 11, 1941.

From the Frank Billings Medical Clinic, the Department of Medicine, University of Chicago.

count was 5.06 million, hemoglobin 92 per cent (Dare), white cell count 7600. Repeated urinalyses were normal. Three histamine tests of gastric secretion, using 0.6 to 0.8 mg. of histamine hydrochloride, disclosed a maximum free acidity of 25, 10, and 0 clinical units respectively. Examination of the feces for occult blood while the patient was on a meat free diet gave results varying from a negative to a strongly positive reaction.

The roentgenologic examination of the stomach on November 28 was reported by the examiner, Dr. Paul C. Hodges, in part as follows (see figure 1):



FIG. 1. Roentgenologic appearance of infiltrative ulcerative syphilis of the antrum of the stomach. (a) Taken with compression applied to the antrum, shows the collection of barium described on the greater curvature side of the antrum and the dilated second portion of the duodenum. (b) is another view of the antrum and the lower body of the stomach with compression, and (c) a view without compression. In (b) nodules outlined by thin layers of barium completely replace the normal rugal pattern in the distal portion of the antrum. In the proximal portion, the nodules of the anterior wall are superimposed on the normal appearing folds of the posterior wall. One of the folds, extending across the antrum from the lesser curvature, divides above and partially overlaps a large mass lying near the greater curvature. The collection of barium along the lesser curvature, distal to the angle, is presumably barium caught between folds. In (c) the irregular narrowing of the antrum caused by the thickening of the walls and the encroachment of the nodules on the lumen is more marked in the distal end where the lesion completely surrounds the lumen.

"There is a frank lesion of some sort in the pyloric antrum which I think almost certainly is a gastric ulcer at the greater curvature with surrounding inflammatory mass and adhesions. The duodenal bulb is normal and the second portion is normal except that it is dilated. I had the impression that there was partial obstruction of the second portion, perhaps by adhesions about the gastric ulcer. The patient weighs only 128 pounds and yet surprisingly the examination was rather difficult because of relaxed abdominal muscles. At times I thought I could make out an ulcer crater at the greater curvature of the antrum. At other times it seemed that this might possibly be an ulcer or diverticulum in the second portion of the duodenum.

"Impression: Frank lesion of some sort involving pyloric antrum and second portion of duodenum, probably gastric ulcer. Am trying to repeat this part of the examination."

"Second roentgen-ray examination: Findings are approximately as before. That the pyloric antrum is frankly abnormal and that the second portion of the duodenum is dilated there can be no doubt. There may possibly be a large shallow ulcer crater on the greater curvature of the pyloric antrum but the appearance is by no means typical.

"Impression: Frank lesion pyloric antrum and probably also second portion of duodenum, nature not determined."

The gastroscopic examination by Dr. Rudolf Schindler on December 9 was described as follows (see figure 2):

"There was half an ounce of stomach contents containing no acid.

"The patient was very coöperative and the whole stomach was seen. The view of the antrum revealed immediately an extensive pathology. The antrum was narrowed by a stiff infiltration and there were reddish nodules protruding from the anterior wall. The circumference of the angulus was infiltrated, also, and within this infiltration two ulcers were seen. The one ulcer toward the lesser curvature was pinkish gray in color with not definitely blending edge, surrounded by a rather flat stiff wall, which was only half a centimeter thick. The mucosa above this wall looked normal. The second ulcer lying in a diffuse infiltrated area had no wall.



FIG. 2. Gastroscopic picture of gastric syphilis, simulating carcinoma. The narrowed slit-like cavity of the antrum is seen in the center. It is surrounded by stiffly infiltrated mucosa. Extensive ulceration is present. At the left lower margin there is a wall-like elevation, rather sharply limited toward the normal mucosa coming into the field from 6 o'clock.

"It was difficult to tell how far the infiltration of the posterior wall extended upward. However, the limiting wall of the lesser curvature was located 13 cm. below the cardia and at 10 cm. below the cardia no infiltration of the posterior wall was visible. The lesser curvature and anterior wall above this area showed an almost complete atrophy, thinning, grayish to white color with many blood vessels.

"Impression: (1) Carcinoma, Type III, of the antrum limited by a wall at the lesser curvature but diffusely infiltrating the posterior wall. (2) Extensive atrophic gastritis. (3) Type III carcinoma usually does not give a good prognosis but in this case the upper margin is so far distant from the cardia that, in my opinion, the attempt of a resection must be made.

"Note: After gastroscopy I learned that the patient has a positive Wassermann. While gastric lues should be considered, notwithstanding, I still feel that this is a neoplastic lesion."

The presence of an ulcerative lesion of the gastric antrum was clearly indicated by the evidence presented. The differential diagnosis involved primarily peptic ulcer, carcinoma and syphilis. The location of the ulcer and its roentgenologic and gastroscopic manifestations did not fit with the diagnosis of benign peptic ulcer.³² On the other hand, the picture was entirely compatible with syphilis or carcinoma. The posi-

tive history favored the former diagnosis; the greater frequency of carcinoma favored the latter. Positive differentiation could be made only by histologic study of the tissue or by continued observation under antiluetic therapy. Surgery was advised because it would give a prompt and decisive answer to the question and also because, if carcinoma were found, the patient would thus have been given the benefit of rather early surgical treatment. Consequently, operation was performed by Dr. Lester Dragstedt December 16, 1940, the tentative diagnosis being (a) gastric syphilis or (b) gastric carcinoma. The abdomen was opened through a right paramedian incision. The peritoneal cavity contained free fluid. The omentum was normal in appearance. The



FIG. 3. Ulcerative gastric syphilis showing the serpiginous configuration of the prepyloric ulcer and, on section, the thickening of the wall. The pylorus is at the left facing the identification tag. The distal edge of the ulcer adjoins the pylorus and is partially hidden by the overlying gastric wall seen on longitudinal section.

serosa over the stomach and duodenum was normal. The cardia and fundus of the stomach were normal to palpation. The gastric antrum was thickened and had a resilient consistency. There were no areas of hardness to suggest carcinoma. Several enlarged lymph nodes were observed along the lesser curvature. A partial gastrectomy was performed.

The pathologic description of the resected specimen (figure 3) is as follows:

"The specimen consists of the lower two thirds of the stomach and the first 3 cm. of the duodenum. The entire antral region including the pylorus is thickened but soft. There are numerous hyperplastic lymph nodes in the attached mesentery. The serosal surface is smooth and shining. At the pylorus the lumen of the stomach is narrowed

to a diameter of 1.7 cm. The proximal mucosa appears slightly edematous, but otherwise normal. Beginning about 5 cm. from the proximal end of the resected specimen on the greater curvature and extending along the anterior wall to the antrum is a nodular irregularity of the mucosa from which region the folds of normal mucosa radiate outward. This nodular area measures 7 cm. in diameter and is continuous with a similar area of involvement in the pyloric and prepyloric regions. The mucosa of the entire prepyloric region, pylorus and upper duodenum is nodular. The gastric wall, however, is soft and pliable. Extending around the pylorus, except for a band of intact mucosa 3 mm. wide, is a shallow ulcer of irregular shape measuring 3.5 by 4.3 cm. in longest diameters. The base of the ulcer is smooth and dark brownish-red. The margins of the ulcer are raised only slightly and there is little apparent infiltration of the mucosa surrounding the ulcer. The base of the ulcer lies in the submucosa and there is no more gross infiltration of the base of the ulcer than there is throughout the entire wall of the antral region of the stomach. The ulcer margins are only very slightly rolled. In the prepyloric region the gastric wall is 8 mm. thick while at the proximal end it is 3 mm. thick. In the thickened region the wall has a glassy appearance similar to, but softer than, that of scirrhous carcinoma."

The important histologic features of the lesion may be seen in figures 4 to 8.

The outstanding characteristics of this gastric lesion are accumulations of inflammatory cells, both diffuse and perivascular; scattered small follicle-like groups of round cells and gummatoid or tuberculoid granulomata; and a large but quite superficial ulcer. Necrosis is evident only on the floor of the ulcer which has a base of very vascular and cellular granulation tissue, topped by a fibrinous membrane. The invading cells are mainly lymphocytes and plasma cells, with quite a few eosinophiles in some regions, and occasional neutrophils. Epithelioid and giant cells are found only in the small granulomata which are invariably closely associated with blood vessels. No organisms (bacteria, yeasts, fungi or spirochetes) can be identified in suitably stained sections.

Perivascular round cells and inflammatory changes in the blood vessels are the lesions most suggestive of syphilis. Many large and small blood vessels, arteries as well as veins, located in all parts of the antral wall, are ringed by lymphocytes and plasma cells. Arteritis is relatively mild although many arteries show, besides the periarteritis, a focal or general proliferative intimitis. In a few small arteries the lumina are appreciably narrowed, and in some of them lymphocytes are scattered through the thickened intimas. Many veins show a similar mild phlebitis. The most conspicuous venous lesions are of two categories, one affecting large veins, deep in the gastric wall; and the other involving small veins and particularly those of the thick submucosa. Multiple and serial sections demonstrate that vascular lesions are focal or segmental and that they are most numerous in the neighborhood of the ulcer.

At first glance the lesions of the larger veins appear to be nodular granulomata, located deep in the submucosa or within the muscle coat (figures 4 and 5). These nodules are composed largely of epithelioid cells, giant cells, lymphocytes and connective tissue. The relationship to veins becomes obvious in sections stained so as to demonstrate elastic tissue (figure 6), and in segments in which a part of the venous wall is intact (figure 7). The pathologic condition is plainly a panphlebitis, with narrowing or obliteration of the lumen by granulomatous tissue. Miliary nodules, presumably small gummata, may be found in the adventitia, among the remnants of the media, or in the tissue filling the lumen. These nodules are aggregates of epithelioid cells which incorporate a few lymphocytes, and often surround a giant cell. They are looser in structure than the classical small tuberculous nodule and the giant cells are more pleomorphic than is usually the case in tuberculosis. No caseation is seen. The appearance of some segments of veins (figure 7) suggests that the inflammatory changes originate in the adventitia, perhaps by extension from the perivascular

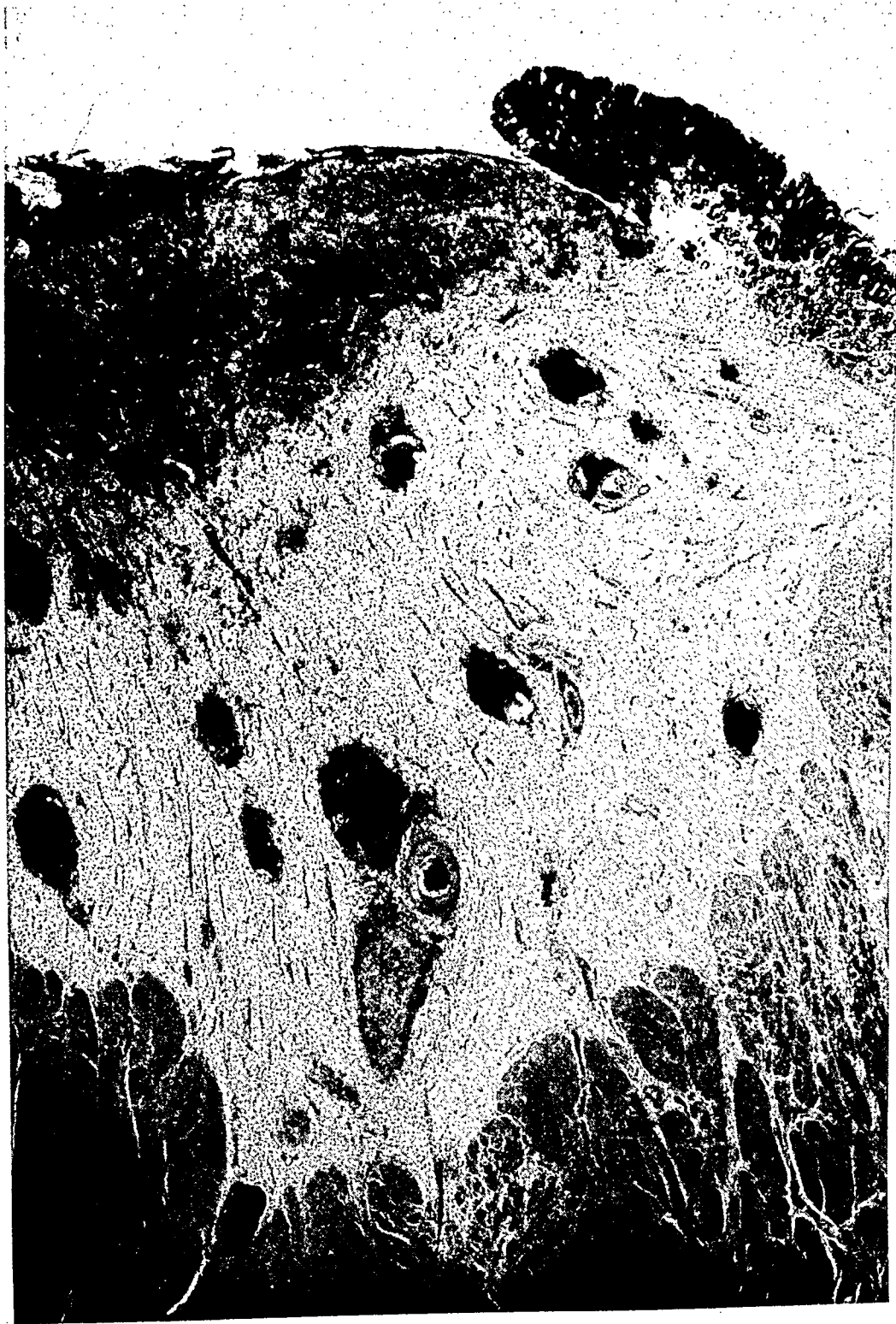


FIG. 4. Syphilitic gastric ulcer. The shallow ulcer has a base of very vascular and cellular granulation tissue and is covered by a membrane rich in fibrin. Note the thick edematous submucosa with follicular aggregates of round cells, the interstitial inflammation of the tunica muscularis, and the gummatous phlebitis affecting a large vein deep in the submucosa. See figures 5, 6 and 7 for details of the phlebitis (in sections of the same vein at different levels) and figure 8 which illustrates a follicular lesion. Hematoxylin and eosin, $\times 16$.



FIG. 5. Panphlebitis in syphilis of the stomach. This photomicrograph of the vein shown in figures 4, 6 and 7 demonstrates the difficulty in identifying the venous wall. The lumen is occluded, and giant cells and two miliary gummata are discernible. Hematoxylin and eosin, $\times 165$.



FIG. 6. Panphlebitis and mild arteritis in syphilis of the stomach. Here the vein shown in figures 4, 5, and 7 can be identified by the darkly stained remnants of its elastic fibers. Two miliary gummata are visible in the granulomatous tissue which replaces the lumen. The periarteritis and mild arteritis are illustrated, as is the interstitial exudate in the tunica muscularis of the vein. Weigert elastic tissue and Van Gieson stain, $\times 110$.

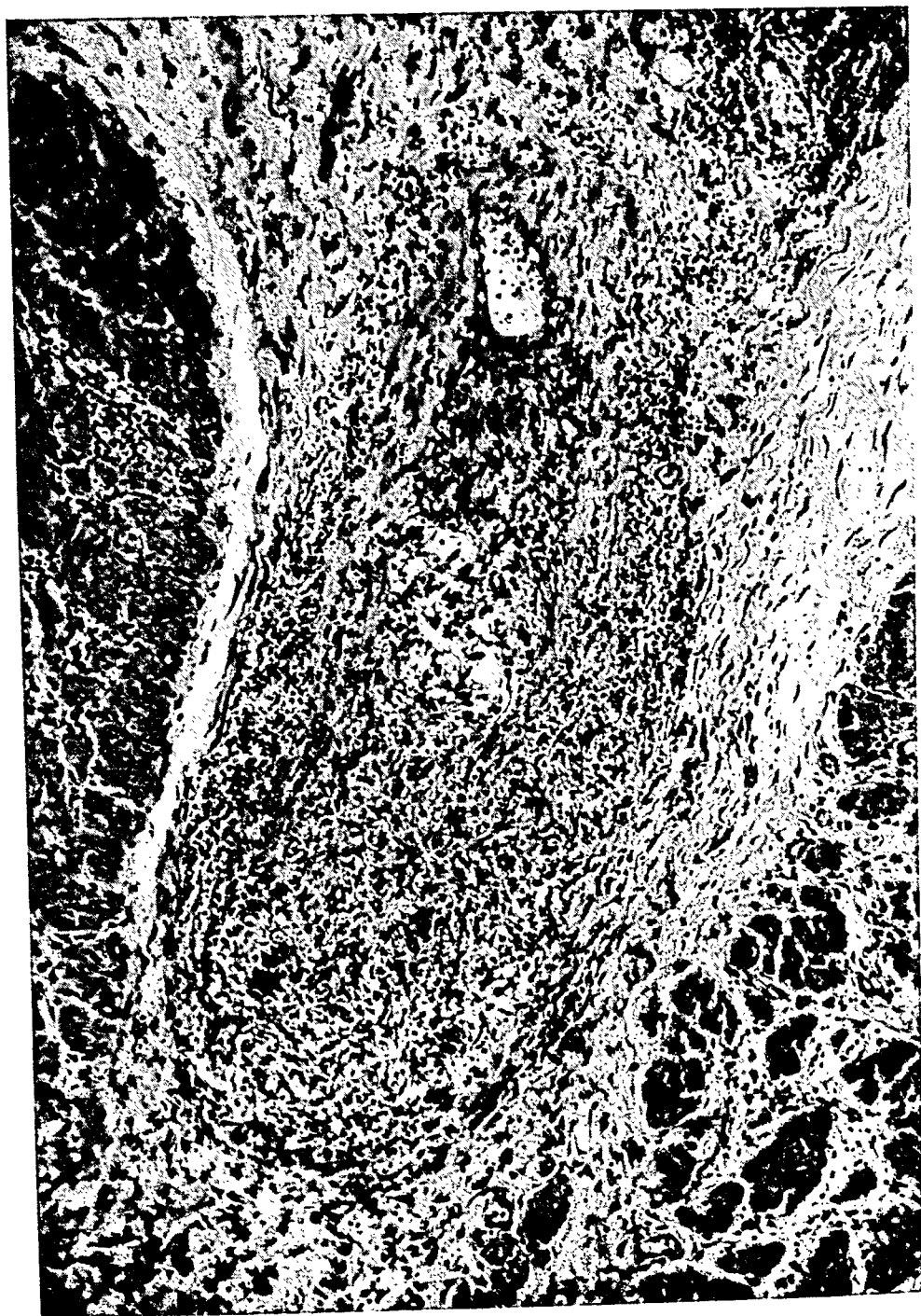


FIG. 7. Pampblebitis in syphilis of the stomach. In this obliquely cut segment of the vein shown in figures 4, 5 and 6 remnants of the media and a small lumen can be recognized, and the appearance suggests invasion of the media and the lumen from the adventitial granuloma. Carbol-thionin, $\times 125$.



FIG. 8. Lymphoid nodule and phlebitis in syphilis of the stomach. A compact nodule of lymphocytes, apparently a lymph follicle, lies near the lower right corner. About it lymphocytes and plasma cells invade the loose stroma and penetrate the wall of a small vein. Some of the small vascular spaces are lymphatics. Weigert elastic tissue and Van Gieson stain, $\times 125$.

lymphatics. There is no proof that thrombosis plays a part in obstructing the lumina of veins.

Some features of the lesions of the smaller veins, too, seem to point to the perivenous lymphatic channels as the primary site of exudation. The central portions of many of the follicle-like lesions so numerous in the submucosa (figure 4) actually seem to be lymph follicles. These globular aggregates of lymphocytes usually lie near or in contact with the veins. They have less compact mantles of loose connective tissue infiltrated by plasma cells and lymphocytes, and often including one or more wide lymphatic vessels. The round cells may invade the vein wall (figure 8). The lumen of the vein may be narrowed or occluded, a fact apparent in sections stained by the Weigert method, in which elastic fibers outline the obliterated channels.

Several other features deserve special comment. The ulcer is nowhere deeply excavated (figure 4), and in some regions bundles of the muscularis mucosae persist in its floor. The mucous membrane is thin in places, with widely separated and atrophic glands. In other regions the glands are simplified and some crypts are cystic. In most sections from the antrum the stroma is loose, invaded by plasma cells and eosinophiles, with occasional lymphocytic follicles. The mucosa is more normal and of the fundic type in sections from the proximal border of the resected segment. Several factors are responsible for the marked thickening of the submucosa (figure 4). These include the granulation tissue and exudate, some general increase of fibrous tissue, and marked edema. Blocking of lymphatic channels is probably a major factor in causing the edema, since wide lymphatic vessels abound in all parts of the wall. Inflammation of the muscle coat is diffuse and extensive beneath the ulcer (figures 6 and 7). It is in this interstitial exudate that eosinophiles are especially numerous. Elsewhere in the muscular layers the infiltration is perivascular, or about nervous elements, and most of the cells are of lymphoid types. Serosal involvement is similar, and is slight except in regions below the ulcer. Here there are larger foci of lymphoid cells in the very edematous peritoneum. The gastric lymph nodes show a lymphocytic hyperplasia with prominent cortical and medullary follicles, and without focal or specific lesions. However, plasma cells invade the areolar tissues about their capsules. Besides a few perivascular foci of round cells the duodenum shows only a superficial catarrhal inflammation.

COMMENT

From the point of view of gross and microscopic pathology, there are no absolutely pathognomonic lesions of gastric syphilis, or indeed of syphilis anywhere in the body. In most cases the diagnosis must rest on presumptive evidence. The characteristics of the gastric lesion here presented are certainly similar to those of reported cases in which there is little doubt of the syphilitic etiology.^{9, 25, 13, 31} Especially noteworthy are the predilection for veins and the unusual types of venous lesions. The diagnostic importance of panphlebitis (or periendophlebitis) in gastric syphilis has recently been reemphasized by Williams and Kimmelstiel.³¹ These authors preferred the term, periendophlebitis, as it stresses the progression of the inflammatory reaction from without to the lumen. Our failure to demonstrate spirochetes is not to be considered a valid argument against syphilis. In most of the late lesions of syphilis the histologic demonstration of spirochetes is rarely unequivocal. All in all, with so many features in common with the best authenticated cases and with so little to hint of any other etiology, it seems quite proper to attribute the unusual gastric lesion of this patient to syphilis. It is almost certainly an example of ulcerated gummatous syphilis, using the term gummatous in its broadest sense as applicable to all late syphilitic lesions which terminate in scarification.

The clinical picture was perfectly compatible with gastric syphilis, but certainly not pathognomonic of such a lesion. The known presence of syphilis and the age of the patient favored the diagnosis, but neoplastic lesions occur not infrequently in individuals of this age and in known syphilitics. The roentgenologist very properly described the abnormal appearance of the outline of the barium-filled gastric antrum, the alterations in the mucosal pattern, and the presence of a crater. The differentiation of the various possible causes of such morphologic alterations is, of course, a conjecture based on the nature and the location of the changes observed and upon consideration of frequency and probability. In this instance the roentgenologist recognized the fact that the lesion was unusual, but did not feel justified in attempting to distinguish between the changes produced by carcinoma, peptic ulcer, syphilis, or other gastric lesions. The soundness of this point of view is evident, we think, from the pathologic features described. The gastroscopist, likewise, and for the same reasons, was unable to make an absolute differentiation. The question as to whether under such circumstances it is better to advise surgical therapy or a trial of antisyphilitic treatment cannot be answered dogmatically. The answer is in part a matter of opinion and in part dependent upon the various conditions present in the case under consideration.

The gastroscopic observation of this case has demonstrated that it may be impossible to differentiate gastroscopically carcinoma and syphilis. The picture seen definitely excluded a benign peptic ulcer, but was rather characteristic of a carcinoma, Type III according to the gross Borrmann classification, consisting of an ulcer within an outspoken stiff infiltration, this infiltration being partially diffuse, partially walled off. It is true that the soft pinkish color of the ulcer floor (characteristically different from the brownish-red color observed in the gross bloodless specimen) was unusual; there was, furthermore, an unusual glistening smoothness of the ulcer floor not mentioned in the protocol. However, there is such a wide range in the various colors and aspects of carcinomatous ulcers that these points seem to be of questionable diagnostic value for future cases.

The gastroscopic literature contains but few reports on gastric syphilis. One of us²¹ observed, in 1923, hourglass formation and extensive gray scarring of the mucosa above the constriction in a case of neurosyphilis and thought these changes might have been the end result of a treated gastric syphilis. In another case numerous small scars were seen in the stump of a stomach, a portion of which had been resected because of proved gastric syphilis.²² Tumefaction has been observed in untreated cases. Dr. Leon Schiff of Cincinnati saw a tumor-like protrusion of the posterior wall of the stomach with multiple small ulcerations in a syphilitic colored girl. Some time after the institution of antisyphilitic treatment, one of us (R. S.) had the privilege of looking into this stomach. A diffusely infiltrating thickening of the posterior wall, indistinguishable from a carcinoma (Type IV) was seen; the ulcer had disappeared. This patient had an uneventful recovery. An almost identical picture was observed by one of us (R. S.) in a colored girl at Cook County Hospital. The carcinoma-like infiltration disappeared entirely under antisyphilitic treatment. Even retrospectively in these two cases the differential diagnosis from carcinoma would have been impossible by the gastroscopic picture; the therapeutic test suggested, and indeed, probably confirmed the diagnosis of gastric syphilis, but no microscopic exami-

nation was possible. The recent German gastroscopic literature⁶ does not contain any report on gastric syphilis, but in the French gastroscopic literature, gastric syphilis is considered to be a frequent finding. Moutier¹⁵ distinguishes gastroscopically four different forms: (1) hemorrhagic, (2) ulcerative, (3) gastritic, and (4) tumorous. Microscopic confirmations of the diagnoses are not presented and the case histories are not always conclusive. However, a colored picture published by Moutier is quite remarkable. Within a nodular, stiff, tumor-like infiltration a large shallow ulcer is seen, the color of which is a dark yellow, quite different from the color seen in benign ulcers and most carcinomata. After treatment this ulcer disappeared. Moutier, however, believes that there is a close relation between cancer and syphilis of the stomach ("un flirt entre la syphilis et le cancer"),¹⁵ and believes that there exist true gastric cancers of syphilitic origin which may be cured.¹⁶ This unique conception may have influenced his gastroscopic interpretation.

The gastroscopic observation and the microscopic study of our case revealed the presence of a severe atrophic gastritis in addition to the tumor formation, a frequent finding, of course, in gastric carcinoma. The atrophic gastritis may account for the histamine-proved anacidity found in a high percentage of cases of gastric syphilis and for the very low acidity, including on one occasion achlorhydria to histamine, demonstrated in the present case.

SUMMARY

The clinical, roentgenologic, gastroscopic and pathologic features of a gastric lesion considered to be ulcerated gummatous syphilis are described and briefly discussed.

BIBLIOGRAPHY

1. BOCKUS, H. L., and BANK, JOSEPH: Upper gastrointestinal disease associated with syphilis, Jr. Am. Med. Assoc., 1928, xc, 175.
2. DOENGES, J. L.: Spirochetes in gastric glands of *Macacus rhesus* and humans without definite history of related disease, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 536.
3. EINHORN, MAX: A new case of syphilitic tumor of the stomach cured by anti-luetic treatment, ANN. INT. MED., 1929, iii, 586.
4. ESTES, W. L., JR.: Syphilis of the stomach, Am. Jr. Surg., 1933, xx, 366.
5. EUSTERMAN, G. B.: Gastric syphilis, Jr. Am. Med. Assoc., 1931, xcvi, 173-179.
6. GUTZEIT, K., and TEITGE, H.: Die Gastroskopie, 1937, Urban und Schwarzenberg, Berlin u. Wien.
7. HARRIS, SEALE and MORGAN, H. J.: The isolation of *Spirochaeta pallida* from the lesion of gastric syphilis, Jr. Am. Med. Assoc., 1932, xcix, 1405-1407.
8. KONJETZNY, G. E.: Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, 1928, Berlin, Vol. IV/2, pp. 1020-1040.
9. KONJETZNY, G. E.: Syphilis des Magens, Dermat. Ztschr., 1933, Bd. lxvi, 289.
10. LEWALD, L. T.: Roentgen diagnosis of gastric syphilis, Jr. Am. Med. Assoc., 1931, xcvi, 179-183.
11. MARC, H.: Gastric syphilis of pseudoneoplastic form: Clinical and radiologic study, Arch. d. mal. de l'app. digestif, 1938, xxviii, 813.
12. McPEAK, C. N.: Syphilis of the stomach with report of an unusual case, Am. Jr. Roentgenol., 1940, xliii, 832-844.
13. MEYER, K. A., and SINGER, H. A.: Syphilis of stomach, with especial reference to its recognition at operation, Arch. Surg., 1933, xxvi, 443.

14. MORTON, C. B.: Syphilis of stomach: Review of literature and report of case, *Arch. Surg.*, 1932, xxv, 880.
15. MOUTIER, FR.: *Traite de gastroscopie*, 1935, Masson & Cie, Paris.
16. MOUTIER, FR., GIRAULT, A., and DEPRAY, CH.: Pseudo-cancers gastriques d'origine syphilitique; leur aspect gastroscopique, *Arch. d. mal. de l'app. digestif*, 1937, xxvii, 637.
17. O'LEARY, PAUL A.: Gastric syphilis, data accumulated from 89 cases, *Am. Jr. Surg.*, 1931, xi, 286-293.
18. PUSCH, LEWIS C.: Syphilis of the stomach; a review of 35 selected cases, *Internat. Clin.*, 1935, i, 56.
19. PUSCH, LEWIS C.: Ulcerative syphilitic lesions of the stomach: Pathologic anatomy of four cases, *Virginia Med. Month.*, 1933, ix, 227.
20. ROWLAND, V. C., and WOLDMAN, E. E.: An instance of syphilis of the stomach, *Am. Jr. Digest. Dis. and Nutr.*, 1935, 1, 822.
21. SCHINDLER, RUDOLF: *Lehrbuch u. Atlas d. Gastroscopie*, 1923, Lehmann, Munich.
22. SCHINDLER, RUDOLF: *Gastroscopy: The endoscopic study of gastric pathology*, 1937, University of Chicago Press, Chicago, Illinois.
23. SCHLESINGER, H.: Present status of clinical aspects of syphilis of the stomach, *Wien. klin. Wchnschr.*, 1929, xlii, 861. Abstracted in *Jr. Am. Med. Assoc.*, 1929, xciii, 885.
24. SINGER, HARRY A.: Syphilis of the stomach with special reference to the significance of spirochetes, *Arch. Int. Med.*, 1933, li, 754.
25. SINGER, HARRY A., and DYAS, FREDERICK G.: Syphilis of the stomach with special reference to certain diagnostic criteria, *Arch. Int. Med.*, 1928, xlii, 718-734.
26. SINGER, H. A., and MEYER, K. A.: Syphilis of the stomach with especial reference to errors in diagnosis, *Am. Jr. Surg.*, 1933, xxi, 1.
27. STOKES, JOHN H., and BROWN, PHILIP W.: Two hundred syphilitic patients whose chief complaint was "stomach trouble." An interpretative analysis of the diagnosis of syphilis in consultant medical practice, *Am. Jr. Med. Sci.*, 1922, clxiv, 867.
28. STRAUSS, H.: Syphilis of the stomach, *Med. Klin.*, 1931, xxvii, 275.
29. TARNOWSKY, GEORGE DE: Surgical limitations in gastric syphilis, *Illinois Med. Jr.*, 1932, lxi, 414.
30. WILLIAMS, CARRINGTON: Syphilis of gastrointestinal tract, *Am. Jr. Surg.*, 1934, xxiv, 834.
31. WILLIAMS, CARRINGTON, and KIMMELSTIEL, PAUL: Syphilis of the stomach, *Jr. Am. Med. Assoc.*, 1940, cxv, 478.
32. PALMER, WALTER LINCOLN: Benign and malignant gastric ulcers: their relation and clinical differentiation, *ANN. INT. MED.*, 1939, xiii, 317.

PAROXYSMAL AURICULAR FIBRILLATION IN ASSOCIATION WITH HIATUS HERNIA; REPORT OF A CASE*

By WILLIAM D. STUBENBORD, M.D., *New York, N. Y.*

PAROXYSMAL auricular fibrillation has been described many times. The inciting factors are numerous, varied, and often difficult to determine. This arrhythmia may take place in the presence of organic heart disease as well as in hearts which show no variation from the normal. Not infrequently, the inciting factor is due to alcoholic drinking or to some gastrointestinal disorder.

The association of hiatus hernia with heart disturbances is now well established. Harrington,¹ in a review of 60 cases of hiatus hernia, had seven cases

* Received for publication June 8, 1942.

which were diagnosed as heart disease. Recently, Gilbert² stated that hiatus hernia may induce attacks of paroxysmal auricular fibrillation, the arrhythmia coming on with the protrusion of the stomach into the esophageal hiatus and disappearing when the stomach slips back into place. The occurrence is mediated through the vagus. An understanding of the vagus and its distribution will enable one to appreciate the association of the esophagus, stomach and heart through the nervous system.

The vagus nerve is composed of parasympathetic efferent, somatic motor (special visceral efferent) and sensory fibers. It arises in the medulla oblongata and passes through the neck and thorax to the abdomen. The right and left branches join to form the esophageal plexus. From this plexus one trunk is formed which goes through the diaphragm on the posterior wall of the esophagus and is distributed to the posterior surface of the stomach. Arising from the esophageal plexus is another branch which passes through the diaphragm on the anterior surface of the stomach.

There are two other branches of the vagus nerve—the superior and inferior cardiac. The superior cardiac arises from the vagus in the neck; the inferior cardiac arises from the vagus as it lies by the side of the trachea and also from the recurrent nerve. All the branches contain parasympathetic efferent and sensory fibers.

During the act of retching and vomiting the branches of the vagus may be stimulated with a resulting excitation of the fibers to the heart, followed by a disturbance of rhythm. Also during severe vomiting, the herniation may be exaggerated with resulting pressure on the lower portion of the esophagus and stimulation of the esophageal plexus.

The following case is being reported because of the occurrence of paroxysmal auricular fibrillation in an individual with hiatus hernia.

CASE REPORT

D. R. J., a male, aged 44, was suddenly taken ill with a rapid irregular beating of the heart. This followed an attack of severe headache, retching and vomiting brought on by an overindulgence in alcohol and food. After considerable retching he complained of a fluttering sensation in the chest and some shortness of breath. The attack lasted for about 48 hours and a normal rhythm was established after he had taken 0.6 gram of quinidine.

The patient stated that since early childhood he had had recurrent attacks of sick headache, unilateral in nature, associated with gastrointestinal upsets and vomiting. After maturity these attacks were brought on by worry, fatigue, or indiscretions in diet or drink.

Between 1922 and 1925, while the patient was in medical school, the headaches became severe and incapacitating. It was during a severe attack that he first developed a peculiar sensation in his chest, this following an episode of vomiting. The sensation disappeared within 24 hours and after this time he felt perfectly well. During every attack of sick headache and vomiting he had thereafter, he noticed this peculiar sensation in the chest associated with an irregularity of the heart. These attacks subsided spontaneously within 24 to 36 hours. In 1932 he began to take digitalis with no appreciable effect on the arrhythmia. In 1941 the patient had a gastrointestinal series done because of a recurrence of indigestion and symptoms suggestive of a peptic ulcer. The roentgenograms showed a paraesophageal hiatus hernia (figure 1). A Graham test done at the same time showed a normally functioning gall-bladder.

The following series of electrocardiograms show the sequence of events which took place during a recent attack. The first electrocardiogram was taken during a routine physical examination of the patient 11 days before this attack and shows a normal sinus rhythm. On inspection of the second and third records it may be seen



FIG. 1.

Feb. 11, 1942

Feb. 22

Feb. 23

Feb. 24

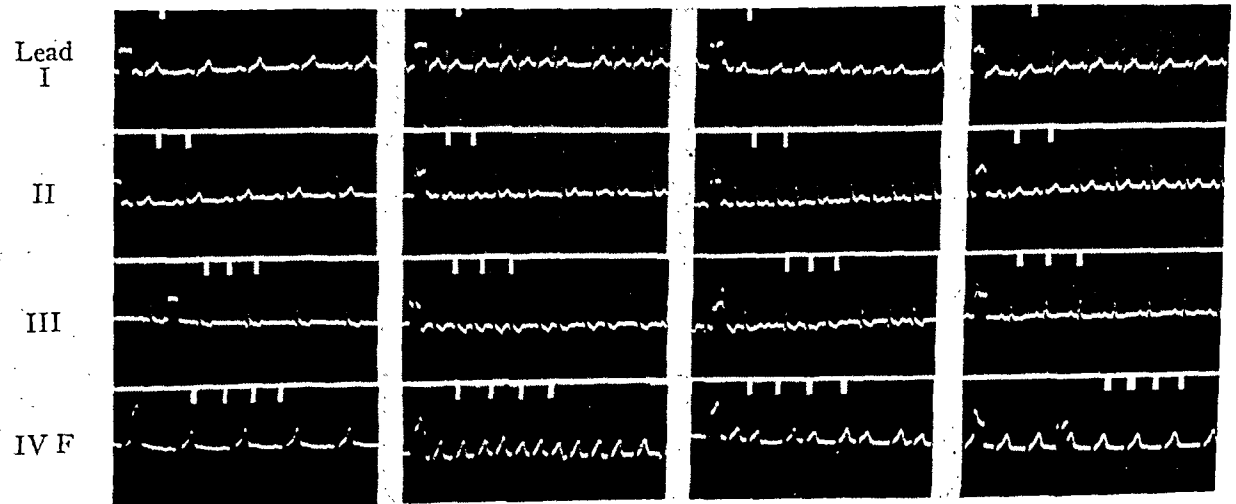


FIG. 2.

that there is auricular fibrillation with electrical alternans. In addition to the fibrillation there are periods of what appear to be nodal coupling and periods in which the ventricular groups are very regular. These may represent auricular fibrillation with regular ventricular rhythm as described by Levy³ and others. The last electrocardiogram of the series shows a return to a normal sinus rhythm 48 hours after the onset of the arrhythmia.

SUMMARY

1. A case of paroxysmal auricular fibrillation occurring in a patient with hiatus hernia is reported.

2. Hiatus hernia should be searched for in a person with paroxysmal tachycardia.

BIBLIOGRAPHY

1. HARRINGTON, STUART W.: Diaphragmatic hernia, Jr. Am. Med. Assoc., 1933, x, 987-994.
2. GILBERT, N. C.: Influence of extrinsic factors on the coronary flow and clinical course of heart disease, Bull. New York Acad. Med., 1942, 83-91.
3. LEVY, R. L.: Auricular fibrillation with regular ventricular rhythm and rate over sixty, Arch. Int. Med., 1926, xxxviii, 116-128.
4. LEWIS, WARREN H.: Anatomy of the human body, by H. GRAY, 1936, Lea & Febiger, Philadelphia, xxiii, 900-904.
5. JACKSON, C. M.: Morris's human anatomy, 1914, P. Blakiston Co., Philadelphia, v, 954-958.
6. BRILL, I. C.: Auricular fibrillation; the present status with a review of the literature, ANN. INT. MED., 1937, x, 1487-1502.

EDITORIAL

VITAMIN DEFICIENCY AND LIVER DISEASE

The relation of vitamin deficiency to liver disease may be approached from two angles: (1) vitamin deficiency as an etiologic factor in the production of liver disease; (2) the rôle of preëxisting liver disease in the development of certain vitamin deficiency states.

An abundance of experimental evidence attests to the etiologic rôle of vitamin deficiency in the production of liver disease. MacLean and Best¹ in 1934 reported that fat was deposited in the livers of rats kept on a high-fat intake and that this fatty deposition could be prevented by giving adequate choline (now generally regarded as a member of the vitamin B complex). Subsequently, György and Goldblatt² produced fatty livers with necrosis in rats maintained on a diet deficient in the vitamin B complex even though supplemented with thiamin, riboflavin, and pyridoxin. The addition to the diet of yeast, a yeast extract, or 2 milligrams of choline a day usually prevented the changes in the liver. Rich and Hamilton³ succeeded in reproducing true cirrhosis of the liver in rabbits fed a deficient diet. The development of cirrhosis was not prevented by the addition of thiamin, riboflavin, pyridoxin, nicotinic acid, or vitamins A, D, and E to the basal diet, whereas a supplement of 5 grams of dry brewer's yeast a day gave full protection.

Interpretation of disease in man in the light of experimental work in animals must be made with the utmost of caution. However, certain clinical observations suggest that vitamin deficiency may be an all-important etiologic factor in fatty liver and cirrhosis of the liver in human beings. Fatty liver is frequently encountered in patients suffering from tuberculous enteritis and peritonitis, in whom decreased food intake and defective absorption from the intestinal tract are prominent features. Furthermore, fatty liver and cirrhosis of the liver are common in alcoholics who are also prone to develop other deficiency diseases such as polyneuritis, pellagra, beriberi, and cheilosis. Wayburn and Guerard⁴ reported multiple peripheral neuropathy in 17 per cent of a large series of cirrhotic patients. Incontrovertible evidence that ethyl alcohol per se can produce cirrhosis or any of the other recognized deficiency states just enumerated has never been established. The trouble with the severe alcoholic is that he forgets to eat, and it seems plausible to assume that these various morbid states to which

¹ MACLEAN, D. L., and BEST, C. H.: Choline and liver fat, *Brit. Jr. Exper. Path.*, 1934, xv, 193.

² GYÖRGY, P., and GOLDBLATT, H.: (a) Hepatic injury on a nutritional basis in rats, *Jr. Exper. Med.*, 1939, lxx, 185; (b) Choline as a member of the vitamin B₂ complex, *Jr. Exper. Med.*, 1940, lxxii, 1.

³ RICH, A. R., and HAMILTON, J. D.: The experimental production of cirrhosis of liver by means of a deficient diet, *Bull. Johns Hopkins Hosp.*, 1940, lxvi, 185.

⁴ WAYBURN, E., and GUERARD, C. R.: Relation between peripheral neuropathy and cirrhosis of the liver, *Arch. Int. Med.*, 1940, lxvi, 161.

an alcoholic is subject are primarily manifestations of vitamin deficiency. Conceivably alcohol may exert a toxic effect in the face of a poor diet, but the rôle of alcohol must be a minor one at best, since all of the deficiency syndromes may develop in total abstainers on deficient diets. Patek⁵ has observed remarkable improvement in patients with cirrhosis who were treated with a diet high in protein, carbohydrates, and vitamins, supplemented with large doses of brewer's yeast and liver extract. Ascites cleared up permanently in a number of his patients. Snell⁶ has reported similar results with a high carbohydrate, high vitamin therapeutic regimen. Thus, there appears to be a significant relationship between nutritional deficiency and cirrhosis of the liver, both from the standpoint of clinical manifestations and from the results of high vitamin therapy in cirrhotics.

Now to turn to the other side of the ledger, the rôle of preëxisting liver disease in the development of certain vitamin deficiency states. Liver disease may contribute to deficiency of the fat-soluble vitamins A and K in one of three ways: (1) failure of proper absorption in patients with jaundice; (2) failure of storage of the vitamin in the diseased liver; (3) disturbance of intermediary metabolism of the vitamin in the damaged liver. In patients with obstructive jaundice or hepatitis, the lack of bile salts in the intestinal tract results in poor absorption of fats and fat-soluble vitamins.

Vitamin A deficiency is recognizable by any one of three methods: dark adaptation test, chemical determination of vitamin A in the blood, and typical pathologic changes such as epithelial metaplasia and keratinization. Defective absorption of vitamin A and carotene has been demonstrated in children with congenital atresia of the bile ducts⁷ and in patients with catarrhal jaundice. These clinical observations receive experimental support in bile fistula rats in which changes in vaginal epithelium were used as a criterion of vitamin A deficiency. Carotene furnishes the chief source of vitamin A in the average diet, and the normal liver converts carotene to vitamin A through the action of an enzyme carotenase. Testing liver slices in vitro, Olcott and McCann⁸ found that a severely damaged liver fails to convert carotene to vitamin A. Low blood levels of vitamin A and a high incidence of night-blindness have repeatedly been described in patients with cirrhosis; while in Africa clinical keratomalacia and epithelial metaplasia of the organs are said to be common in association with various forms of liver disease. Therapy should consist in large doses of vitamin A administered orally along with bile salts or large parenteral injections of vitamin A. Little improvement is to be expected from a high carotene intake in patients with severe liver damage.

⁵ PATEK, A. J., and POST, J.: Treatment of cirrhosis of the liver by nutritious supplements rich in vitamin B complex, *Jr. Clin. Invest.*, 1941, xx, 481, 505.

⁶ SNELL, A. M.: Recent advances in treatment of hepatic disease, *Minnesota Med.*, 1940, xxiii, 551-556.

⁷ ALTSCHULE, M. D.: Vitamin A deficiency in spite of adequate diet in congenital atresia of bile ducts and jaundice, *Arch. Path.*, 1935, xx, 845.

⁸ OLCOTT, H. S., and MCCANN, D. C.: Carotenase: The transformation of carotene to vitamin A in vitro, *Jr. Biol. Chem.*, 1931, xciv, 185.

The recognition of the etiologic rôle of vitamin K deficiency in the hemorrhagic diathesis so common in patients with jaundice represents one of the most important contributions to medical knowledge within the past ten years. The hemorrhagic tendency in jaundiced patients has been conclusively shown to be due to lowered plasma prothrombin which in turn results from inadequate absorption of fat-soluble vitamin K, failure of the severely damaged liver to utilize vitamin K in the formation of prothrombin, or a combination of these two conditions. Several satisfactory methods for measuring the prothrombin content or prothrombin time of plasma are now available; the prothrombin level is regarded as an index of the status of the individual with respect to vitamin K. The failure of jaundiced patients to absorb vitamin K may be controlled in one of the following ways: oral administration of bile salts along with crude natural sources of vitamin K such as alfalfa and fish meals or with a synthetic fat-soluble derivative of vitamin K such as 2-methyl-1, 4-naphthoquinone (1-4 mg. a day); oral administration of a water-soluble vitamin K derivative such as 4-amino-2-methyl-1-naphthol which does not require the aid of bile salts for its absorption; parenteral administration of synthetic compounds, either fat-soluble or water-soluble. If the liver is so severely damaged that it cannot produce prothrombin in spite of an adequate supply of vitamin K, bleeding will not be influenced by any of the three methods of administering vitamin K which have just been described and the prognosis becomes extremely grave. Under such circumstances, we must resort to transfusion of freshly drawn blood to supply prothrombin directly. The full understanding and proper application of these principles by surgeons and internists alike will go far toward decreasing risk from hemorrhage in jaundiced patients. The routine developed by Andrus and Lord⁹ for the preoperative management of a jaundiced patient with lowered prothrombin may be taken as a practical illustration: If the jaundiced patient is bleeding on admission, he is given transfusions as a means of restoring blood lost and at the same time of administering prothrombin directly. All patients with prothrombin levels below 70 per cent (Smith-Warner-Brinkhous method) receive 2 mg. of 2-methyl-1, 4-naphthoquinone intramuscularly and the response after 24 and 48 hours is noted. If the level is still below 70 per cent, the injection is repeated every three days until normal plasma prothrombin value is restored; at most two or three injections will suffice unless severe liver damage is present. Injections may be given daily without hesitation, for there is no evidence that an excess of vitamin K will increase the prothrombin level above normal and thereby promote abnormally rapid clotting of the blood.

In addition to the special functions of the liver with reference to vitamins A and K, the liver is known to serve as a storage depot for the majority of vitamins (A, B-complex, C, D, K) and probably provitamins as well.

⁹ ANDRUS, W. D., and LORD, J. W.: Correction of prothrombin deficiency by means of 2-methyl-1, 4-naphthoquinone injected intramuscularly, *Jr. Am. Med. Assoc.*, 1940, cxiv, 1356.

Hence, patients with severe liver disease are bound to have inadequate reserves and are, therefore, more likely to develop outspoken manifestations of vitamin deficiency under the added strain of a severe infection or curtailment of food intake. It would seem to be established beyond the shadow of a doubt that vitamin deficiency has an important rôle in the etiology of liver disease and, conversely, that preëxisting liver disease predisposes toward the development of numerous and varied manifestations of vitamin deficiency.

W. H. B.

REVIEWS

Encephalitis; A Clinical Study. By JOSEPHINE B. NEAL, A.B., M.D., Sc.D., F.A.C.P.
563 pages; 16 × 23.5 cm. Grune and Stratton, New York. 1942. Price, \$6.75.

This book on encephalitis is a fine piece of medical literature. The print is clear and legible, the mechanics of book-making well thought out, and the medical contents should be read, digested, and retained by anyone interested in the realm of encephalitis in its various manifestations.

Dr. Neal, fortunately, has had the benefit of a large financial grant, made possible by William J. Matheson, who was a victim of chronic encephalitis. Coupled with her own tremendous fund of medical experience, she has not hesitated to select as contributors several others, all of whom are well known in their respective fields.

In Chapter One, she discusses encephalitis and includes the various virus types. In Chapter Three, the neurological complications are discussed; in Chapter Four, the clinical course of epidemic encephalitis. The psychiatric sequelae are discussed by Dr. Rosner, and the behavior disturbances in childhood by Dr. Lauretta Bender. Dr. Bender has also had a great deal of experience with these encephalidides and their neuropsychiatric manifestations.

Although this book is captioned "A Clinical Study of Encephalitis," there is one fine chapter, "Number Nine," written by Dr. Lewis D. Stevenson, in which he elaborates upon the various types of encephalitis, including congenital anomalies, infections, other viruses, parasitic, purulent, and encephalopathies due to the drugs, toxins, disturbances in the hemopoietic systems and avitaminoses. The bibliography is moderately full in this chapter, but since it is not intended to be a complete description of the various ramifications or pathology of the encephalidides, it is not to be considered adequate. To anyone interested, however, there is a sufficient bibliography to give one all the necessary leads. Mention of the several degenerative forms might have included the work of American authors from 1932 on.

This book is to be most highly recommended to students, interns, and general practitioners, as well as to those who work in the field of neuropathology and neuropsychiatry.

L. F.

Fever Therapy. By WALTER M. SIMPSON, M.D., and WILLIAM BIERMAN, M.D.
486 pages; 16 × 24 cm. Paul B. Hoeber, Inc., New York. 1937. Price, \$5.00.

This volume is a compilation of the reports read at the First International Conference on Fever Therapy held in 1937. As stated in the preface, only abstracts of the original papers are published in this book, due to the fact that the papers were so numerous and so long that printing of all of the papers and of the discussions would require several volumes. This is a serious fault with the book, namely, that only from one to three pages are devoted to the subject matter and this is often inadequate. All of the authors are convinced of the value of fever therapy (pyretotherapy) and in some instances make extravagant claims. Thus regarding the treatment of early syphilis, Simpson and Kendall state "Fever therapy alone or chemotherapy alone, as applied to the control groups of patients in this study, was inadequate in a high proportion of cases"; and Neymann states that a few treatments of fever plus arsphenamine and bismuth "will cure most patients with early syphilis promptly, surely and permanently. Most cases of syphilis can thus be aborted in one or two months." It is my opinion that such statements are unwarranted and far too positive and can be made only after an observation period of from 10 to 20 years.

It is to be hoped that this form of abortive treatment will prove satisfactory, but in the past few decades some such claims have been made by others, only to be found false. In general this volume is a valuable addition to the books on fever therapy as it gives résumés of papers of all the leading investigators in this field.

H. M. R.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Sexual Glands of the Male. Reprinted from Oxford Loose-Leaf Urology. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S. Collaborators: FRANK HINMAN, A.B., M.D., F.A.C.S., DONALD R. SMITH, A.B., M.D., and ROBERT GUTIERREZ, A.B., M.D., F.A.C.S. 619 pages; 24 × 16.5 cm. 1942. Oxford University Press, New York. Price, \$10.00.

Rehabilitation of the Tuberculous. By H. A. PATTISON, M.D., F.A.C.P. 186 pages; 23.5 × 15.5 cm. 1942. The Livingston Press, Livingston, Columbia County, New York. Price, \$2.50.

The Treatment of Shock. By R. W. RAVEN, F.R.C.S. (Major, R.A.M.C.). 96 pages; 17 × 11 cm. 1942. Oxford University Press, New York. Price, \$1.50.

Tropical and Sub-Tropical Diseases. By C. H. BARBER, D.S.O.—M.A., D.M. (Oxon), M.R.C.S., L.R.C.P. 189 pages; 17 × 10.5 cm. 1942. Oxford University Press, New York. Price, \$1.50.

Amputations and Artificial Limbs. By R. D. LANGDALE-KELHAM, M.R.C.S., L.R.C.P., and GEORGE PERKINS, M.C., F.R.C.S. 96 pages; 17 × 11 cm. 1942. Oxford University Press, New York. Price, \$1.50.

Religion and Health. By SEWARD HILTNER. 292 pages; 21 × 14 cm. 1943. The Macmillan Company, New York. Price, \$2.50.

Outline of Psychiatric Case Study. A Practical Handbook. Second Edition. By PAUL WILLIAM PREU, M.D. 279 pages; 19 × 13 cm. 1943. Paul B. Hoeber, Inc., New York. Price, \$2.75.

Indigestion. Its Diagnosis and Management. By MARTIN E. REHFUSS, M.D., and SUTHERLAND M. PREVOST. 556 pages; 24 × 16 cm. 1943. W. B. Saunders Co., Philadelphia. Price, \$7.00.

A Handbook of Allergy for Students and Practitioners. By WYNDHAM B. BLANTON, M.A., M.D., Litt.D. 190 pages; 23.5 × 15 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, \$3.00.

Familial Nonreaginic Food-Allergy. By ARTHUR F. COCA, M.A. 160 pages; 22.5 × 15 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, \$3.00.

Understand Your Ulcer. By BURRILL B. CROHN, M.D. 199 pages; 22 × 14 cm. 1943. Sheridan House, New York. Price, \$2.50.

COLLEGE NEWS NOTES

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,217 Fellows and Associates of the College on active military duty. Herewith are reported the names of 104 additional members, bringing the grand total to 1,321.

Theodore J. Abernethy
William B. Adamson
William H. Algie
F. Peel Allison
Charles L. Anderson

Ralph G. Ball
Maurice C. Barnes
Francis L. Barthelme
Lewis B. Bates
Zacharias Bercovitz
Elton R. Blaisdell
Morris Block
William W. Bondurant, Jr.
Ernest L. Boylen
Howard G. Bruenn
George W. Burnett

George A. Cann
Louis H. Charney
Richard J. Clark
Milton H. Clifford
Stuart R. Combs

Einar R. Daniels
J. Dwight Davis
Herman F. DeFeo
Francis G. Dickey
Preston V. Dilts
Ira Dixson
Frederic G. Dorwart
Willard G. Drown
Kenneth L. Druet
Alfred W. Dubbs
Robert B. Durham

F. George Elliott
Ralph A. Elliott
Earl B. Erskine

James M. Faulkner
Henry D. Fearon
Lucian M. Ferris

Elmer S. Gais
Leon J. Galinsky
Edward A. Greco
David S. Greenspun

Karl B. Hanson
George F. Harsh
John Harvey
Lyle E. Heavner
Philip S. Hench
J. Warren Hundley, Jr.

William K. Ishmael

Carl A. Johnson
Clarence E. Johnson
Hartwell Joiner

Edward R. H. Kurz

Lee H. Leger
George L. Leslie
Eugene J. Lippschutz
Robert E. Lyons, Jr.

James M. MacMillan
John J. Maisel
Arthur A. Marlow
Gilbert H. Marquardt
John W. Martin
Edward de S. Matthews
Edward Matzger
Charles K. Maytum
Ronald J. McNamara
Harry D. Miller
John Minor
Sylvan E. Moolten
Alvin E. Murphy

J. Ernest Nadler
J. Marshall Neely

Andrew J. Parker

Harold W. Potter
Vernon E. Powell

Harold L. Rakov
Paul H. Revercomb
Lee Rice
Andrew I. Rosenberger
J. Griswold Ruth
Benjamin H. Rutledge

S. Marion Salley
Robert L. Schaefer
Curt P. Schneider
Thornton Scott
Joseph H. Shaffer
Paul L. Shallenberger
Harry W. Shuman
Walter M. Solomon

Dale C. Stahle
Charles W. Steele
Robert E. Stone
William H. Stoner
George W. Stuppy
Verne W. Swigert

Henry M. Tabachnick
Floyd C. Taggart
Jan H. Tillisch
Herman Tarnower

Aloysius Vass

Harry A. Warren
J. Harold Watkins
Walter L. Winkenwerder
Zolton T. Wirtschafter

Dr. Ben R. Heninger, F.A.C.P., formerly of New Orleans, La., was retired from active military duty, January 31, 1943, for physical disability. Dr. Heninger is now located at Pass Christian, Miss.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

- Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—“Therapeutics of Infancy and Childhood,” Vol. IV and Index Vol.;
Dr. Beverley R. Tucker, F.A.C.P., Richmond, Va.—“Tales of the Tuckers.”

Reprints

- Dr. Nathan Bloom, F.A.C.P., Richmond, Va.—4 reprints;
Dr. George B. Dorff, F.A.C.P., Brooklyn, N. Y.—4 reprints;
Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—1 reprint;
Manfred Kraemer, F.A.C.P., Major, (MC), U. S. Army—2 reprints;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Nathaniel E. Reich (Associate), Brooklyn, N. Y.—5 reprints;
Dr. Maurice S. Segal (Associate), Boston, Mass.—3 reprints;
Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Clarence M. Trippe, F.A.C.P., Asbury Park, N. J.—1 reprint;
Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn.—7 reprints;
Joseph H. Whiteley, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint.

Dr. Ernest E. Hadley, F.A.C.P., Washington, D. C., has contributed copies of his publications, “An Experiment in Military Selection” and “Military Psychiatry,” to the College Library of Publications by Members.

A. C. P. REGENTS AND COMMITTEES WILL MEET APRIL 3-4, 1943

The regular Spring meeting of the College Committees and of the Board of Regents will be held at the College Headquarters in Philadelphia on the week-end of

April 3-4, 1943. At this meeting the customary business transacted at the Annual Sessions will receive attention. The Committee on Credentials will review the credentials of all candidates for Associateship and for Fellowship, and make recommendations for action by the Regents. Candidates must be proposed thirty days in advance of action.

NATIONWIDE PROGRAM FOR POSTGRADUATE SEMINARS BEING ORGANIZED FOR MEDICAL OFFICERS IN THE ARMED FORCES

In accordance with action approved by the Board of Regents of the American College of Physicians, Philadelphia, December 13, 1942, and since approved by the American Medical Association and the American College of Surgeons, these three great medical societies have combined in a program of postgraduate seminars to be conducted at Naval and Army medical installations in various parts of the country. A committee of three, one from each organization, consisting of Dr. William B. Breed, Boston, for the American College of Physicians, Dr. Alfred Blalock, Baltimore, for the American College of Surgeons, and Dr. Edward L. Bortz, Philadelphia, for the Council on Scientific Assembly of the American Medical Association, has been appointed by the respective societies, with power to act in the development of a program and putting it into action. Each College has appropriated \$5,000.00, and the American Medical Association, \$10,000.00. Dr. Bortz will be the Chairman and Dr. Breed the Secretary-Treasurer.

This is an extension of the work the American College of Physicians already has conducted in the field of internal medicine through the past two years. The new program will be a much larger and more inclusive one, covering the whole field of medicine.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows have become Life Members of the College since January 1, 1943. This is an especially auspicious time for physicians in private practice to take out life memberships; income from private practice is probably at its peak, and the College plan of life membership provides a means of underwriting one's dues during his most productive years while his income is highest, thus avoiding the burden of dues later in life. All life membership fees are deposited in the permanent Endowment Fund of the College, thus contributing to the stability and perpetuity of the organization.

Dr. Ralph K. Hollinshed, Westville, N. J.
Dr. Ranald E. Mussey, Troy, N. Y.
Dr. Eliah Kaplan, New Castle, Pa.
Dr. G. B. Kramer, Youngstown, Ohio
Dr. Spencer A. Folsom, Orlando, Fla.
Dr. Robert A. C. Wollenberg, Detroit, Mich.
Dr. Edgar F. Kiser, Indianapolis, Ind.
Dr. William Corr Service, Colorado Springs, Colo.
Dr. Harry Gauss, Denver, Colo.
Dr. Harold E. Himwich, Albany, N. Y.
Dr. Willard B. Howes, Detroit, Mich.
Dr. Joseph C. Placak, Cleveland, Ohio
Dr. Harold Riche Roehm, Birmingham, Mich.
Dr. George E. Baker, Casper, Wyo.
Dr. Charles S. Bluemel, Denver, Colo.
Dr. Samuel A. Loewenberg, Philadelphia, Pa.

NEW ENGLAND REGIONAL MEETING HELD IN BOSTON, FEBRUARY 5, 1943

The second annual Regional Meeting for the New England States was held in Boston, Friday, February 5, at Hotel Statler under the general chairmanship of Dr. William B. Breed, F.A.C.P., Governor for Massachusetts, and with the coöperation of the Governors of the New England States, Dr. Charles H. Turkington, F.A.C.P., Connecticut; Comdr. Eugene H. Drake, F.A.C.P., Maine; Dr. Harry T. French, F.A.C.P., New Hampshire; Dr. Alexander M. Burgess, F.A.C.P., Rhode Island; and Dr. Ellsworth L. Amidon, F.A.C.P., Vermont.

Dr. Earle Chapman, F.A.C.P., Boston, was Chairman of the Committee on Arrangements, and Dr. Roger I. Lee, F.A.C.P., Boston, was Chairman of the Committee on Program.

The scientific program was as follows:

MORNING SESSION—10:00 A.M.

Presiding Officer

REGINALD FITZ, F.A.C.P.

*Lecturer on History of Medicine and Assistant to the Dean of the Faculty of Medicine
Harvard Medical School*

"Immersion Foot." James C. White, Commander, (MC), U.S.N.R.

"Observations on Immunity of Mumps." John Franklin Enders, Associate Professor of Bacteriology and Immunology, Harvard Medical School.

"Personnel Selection." C. W. Heath, W. L. Woods, L. Brouha, C. C. Seltzer and A. V. Bock, from the Grant Study, Hygiene Department, Harvard University.

"Post Concussion Syndrome." Derek Ernest Denny-Brown, F.R.C.P., Professor of Neurology, Harvard Medical School.

"Gonococcal Infections." Hugh J. Morgan, F.A.C.P., Brigadier General, (MRC), U. S. A., Washington, D. C.

"Sub-Clinical Thiamin Deficiency." Joseph Wiley Ferrebee, Associate Professor of Dental Medicine, Harvard Medical School.

"The Flight Surgeon." David N. W. Grant, Brigadier General, Air Surgeon, Army Air Force, Washington, D. C.

AFTERNOON SESSION—2:00 P.M.

Presiding Officer

JAMES HOWARD MEANS, F.A.C.P.

Jackson Professor of Clinical Medicine, Harvard Medical School

"The Relation of the Carrier to Epidemic Meningitis." John Howard Mueller, Professor of Bacteriology and Immunology, Harvard Medical School.

"Seasickness." Robert S. Schwab, Lieutenant Commander, (MC), U.S.N.R.

"The Present Status of Electro-encephalography." Frederic Andrew Gibbs, Instructor in Neurology, Harvard Medical School.

"Problems of Immunity to Bacillary Dysentery." Rene Jules Dubos, George Fabian Professor of Comparative Pathology and Professor of Tropical Medicine, Harvard Medical School.

"Principal Disqualifying Lesions Encountered in Military Service." Julien E. Benjamin, F.A.C.P., Lieutenant Colonel, (MRC), U. S. A., Chief of Medical Service, Lovell General Hospital, Fort Devens, Mass.

"Hearts Young and Old Under the Strain of War." Paul Dudley White, F.A.C.P., Lecturer in Medicine, Harvard Medical School.

"Primary Atypical Pneumonia." Francis G. Blake, F.A.C.P., Sterling Professor of Medicine, and Dean, Yale University School of Medicine.

"Nutrition and Resistance." Frederick John Stare, Assistant Professor of Nutrition, Harvard Medical School.

"High Protein Diet; Clinical Considerations." George Widmer Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School.

A luncheon at the Tavern Club was given by Drs. Breed and Lee in honor of Major General James C. Magee, Surgeon General of the U. S. Army, and other high-ranking officers from the Army Air Force and the Navy Medical Corps.

Many acclaimed the program as the best they had ever attended anywhere. Manuscripts of the papers will be obtained as far as possible and published in the *Annals of Internal Medicine*.

The evening dinner meeting, at which Dr. Breed acted as toastmaster, was addressed by Dr. James E. Paullin, President of the College, Atlanta, Dr. Ernest E. Irons, President-Elect, Chicago, Brigadier General David N. W. Grant, Air Surgeon, Army Air Force, Washington, Brigadier General Hugh J. Morgan, U. S. Army, Washington, Capt. William J. C. Agnew, representing the Surgeon General of the U. S. Navy, who was unable to be present, and by Major General James C. Magee, Surgeon General of the U. S. Army. General Magee reviewed the progress and problems in the medical service of the Army and gave many interesting facts concerning his recent extended trip to the British Isles and to North Africa.

Among other special guests at the dinner meeting were Dr. George Morris Pie, Secretary General, Philadelphia, Mr. E. R. Loveland, Executive Secretary, Philadelphia, Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, Philadelphia, George H. Lathrope, Governor for New Jersey, Newark, Dr. Asa L. Lincoln, Governor for Eastern New York, New York City, Dr. Nelson G. Russell, Sr., Quarry for Western New York, Buffalo, Dr. Hugh A. Farris, Governor for the Maritime Provinces, St. John, Col. William E. Shambora, Ground Surgeon, U. S. Army, Washington, Capt. Herbert L. Kelley, District Medical Officer of the First Naval District, Boston, Col. John J. Reddy, Chief of the Medical Branch, First Service Command, Boston, Dr. Arthur W. Allen, Regent of the American College of Surgeons, Boston, Dr. James Howard Means, Past President of the College, Boston, Dr. Reginald Fitz, Regent of the College, Boston, and others.

To this meeting were invited as guests medical officers of the Army, Navy, and U. S. Public Health Service, especially those stationed in the New England area. An analysis of the registration follows:

	Fellows	Associates	Guests	Total
M. C., U. S. Army	7	4	77	88
M. C., U. S. Navy	17	3	32	52
U. S. Public Health Service .	2	—	1	3
<hr/>				
Total, Service Men	26	7	110	143
Civilian Physicians	111	19	38	168
<hr/>				
Total	137	26	148	311

Forty per cent of the College membership in New England was in attendance. An analysis of the geographic distribution is as follows:

Connecticut	45
Maine	8
Massachusetts	170
New Hampshire	8
Rhode Island	40
Vermont	6
Other states and countries outside of New England, including the District of Columbia, Florida, Georgia, Illinois, Maryland, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Virginia, New Brunswick (Canada), Brazil, Chile, Peru and Venezuela	34

A. C. P. REGIONAL MEETING TO BE HELD IN NEW ORLEANS

APRIL 16-17

A Regional Meeting for the States of Louisiana, Mississippi, Arkansas, and Eastern Texas will be held at New Orleans at the new State Charity Hospital on Friday and Saturday, April 16-17, under the direction of Dr. Edgar Hull, Governor for Louisiana, with the aid and assistance of the College Governors for the States mentioned, namely, Dr. John G. Archer, Greenville, Miss., Dr. Oliver C. Melson, Little Rock, Ark., and Dr. M. D. Levy, Houston, Tex. Dr. Grace Goldsmith, New Orleans, is Chairman of the Committee on Clinics and Dr. John H. Musser, New Orleans, is Chairman of the Committee on Scientific Essays.

Friday and Saturday mornings will be devoted to clinics. A luncheon will be held on Friday at noon and a dinner, Friday evening. At this dinner meeting ranking authorities from the Army and Navy will present timely and interesting addresses. The meeting will end Saturday noon with a clinical pathological conference, at which the clinician will be Dr. James E. Paullin, President of the College.

All medical officers in the Armed Forces, who are stationed in the participating States, are cordially invited to attend.

By the time this notice appears in the Annals of Internal Medicine the formal programs will be organized and ready for distribution. They will be sent to all members in the States concerned and to all Army and Navy installations within those States. Other members interested may obtain copies on request from the Executive Offices of the College.

Physicians expecting to remain over night in New Orleans should apply for reservations at hotels and for reservations on trains as far in advance as possible. Address applications for hotel reservations to Dr. B. J. DeLaureal, Committee on Hotels, 3439 Prytania St., New Orleans, La.

MIDDLE ATLANTIC REGIONAL MEETING OF THE COLLEGE

On April 24, 1943, under the chairmanship of Dr. Wallace M. Yater, College Governor for the District of Columbia, and with the combined direction of Dr. Wetherbee Fort, Acting Governor for Maryland, Dr. J. Edwin Wood, Jr., Acting Governor for Virginia, Dr. Albert H. Hoge, Governor for West Virginia, Dr. Paul Whitaker, Governor for North Carolina, and Dr. Lewis B. Flinn, Governor for Delaware, a Regional Meeting for the States mentioned will be held in Washington, D. C.

Every speaker on the program is a medical officer from the Army or Navy and an authority on his subject.

The morning session will be held at the Walter Reed General Hospital and the afternoon session, at the National Naval Medical Center at Bethesda.

Complete programs may be obtained from the Executive Offices of the College, 4200 Pine St., Philadelphia, Pa.

PROGRAM

MORNING SESSION

10:00-12:30

Walter Reed General Hospital
Washington, D. C.

1. Periarteritis Nodosa: Certain Clinical and Roentgenologic Features.
Majors A. O. Hampton and Louis A. M. Krause.
2. Clinical Diagnosis of Lumbar Intervertebral Disc Lesions.
Lt. Col. R. Glenwood Spurling.
3. Contrast Visualization in the Diagnosis of Intrathoracic Disease.
Major George P. Robb.
4. Clinical Report on Primary Atypical Pneumonia.
Capt. Dale C. Stahle.
5. Histaminic Cephalalgia.
Lt. Col. Louis E. Lieder.
6. Simplification of Treatment of Diabetes and Diabetic Coma.
Capt. Lazarus L. Pennock.
7. Malaria in the Army.
Lt. Col. Thomas T. Mackie.
8. The Typhus Problem.
Col. Harry Plotz.
9. Contact Dermatitis.
Major Zeno N. Korth.

LUNCHEON

AFTERNOON SESSION

2:30-5:00

U. S. Naval Hospital
National Naval Medical Center
Bethesda, Md.

1. An Evaluation of the Surgical Treatment of Arterial Hypertension.
Capt. Winchell McKendree Craig.
 2. Coronary Heart Disease.
Comdr. Arthur M. Master.
 3. Experiments on Underwater Concussion.
Capt. F. C. Greaves.
 4. Practical Considerations in the Use of Blood Derivatives.
Comdr. L. R. Newhouser.
 5. The Use of Sulfadiazine in the Treatment of Meningococcus Carriers.
Lt. F. S. Cheever.
 6. Medical Problems Arising from the Return of Military and Naval Personnel from the Tropics.
(Author to be announced.)
 7. The Importance of Sub-groups and the Rh Factor in Blood Transfusions.
Lt. J. J. Engelfried.
- Demonstrations:
- The Electron Microscope.
Comdr. R. H. Drager.
 - Blood Derivatives.
Comdr. L. R. Newhouser.
 - Blood Grouping.
Lt. J. J. Engelfried.

The Regional Meeting will conclude with a Dinner Meeting in the evening at a down town hotel. Many distinguished guests from among Officers of the College and ranking officials of the Armed Forces will be present. Short addresses will be made by Dr. James E. Paullin, President of the College, Rear Admiral Ross T. McIntire, Surgeon General of the U. S. Navy, Major General James C. Magee, Surgeon General of the U. S. Army, and others.

Dr. Paul G. Boman, F.A.C.P., Duluth, has been named President of the Minnesota Society of Internal Medicine and Dr. Bayard T. Horton, F.A.C.P., Rochester, Vice President.

Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., was recently renamed Secretary of the Mayo Clinic staff.

Dr. Robert P. McCombs (Associate), Nashville, Tenn., is conducting a ten-week course in internal medicine for physicians in Hamilton County (Tenn.) under the auspices of the county medical society.

Dr. John H. Fitzgibbon, F.A.C.P., Portland, Ore., spoke on "Oregon Medical Service and Situation in Kaiser Shipyards" at a meeting of the Annual Secretaries' Conference of the Indiana State Medical Association in Indianapolis, January 24, 1943.

On March 11, Dr. Clarence E. de la Chapelle, F.A.C.P., New York, N. Y., spoke on "Management of Acute Cardiovascular Emergencies" at a meeting of the Columbia County Medical Society in Hudson, N. Y., and on March 25, Dr. Norman Plummer, F.A.C.P., New York, N. Y., will speak on "Newer Chemotherapeutic Methods."

The Alumni Society of the New York City Hospital has established the James R. Lisa Award. The award will be given for meritorious work in research medicine done in the laboratories of the Hospital under Dr. Lisa's direction and will be made by him at appropriate times to the worker he selects as being worthy. The prize will consist of a medallion or parchment and of an honorarium of several hundred dollars. Dr. Lisa has been a Fellow of the College since 1935.

The 6th Annual Roger S. Morris Memorial Lecture of the University of Cincinnati College of Medicine was delivered January 8, 1943, by Hugh J. Morgan, F.A.C.P., Brigadier General, (MC), U. S. Army. General Morgan spoke on "Reflections of an 'Irregular' Army Medical Officer."

Dr. Paul S. Rhoads, F.A.C.P., Evanston, Ill., discussed "Nonspecific Pneumonia: Report of 100 Cases" and Dr. Samuel J. Lang, F.A.C.P., Evanston, discussed "Adrenal Cortical Insufficiency and Its Treatment" at a meeting of the North Shore Branch of the Chicago Medical Society on February 2, 1943.

Dr. Eugene M. Landis, F.A.C.P., Head of the Department of Internal Medicine of the University of Virginia, has resigned to become George Higginson Professor of Physiology at Harvard Medical School on July 1, 1943.

Dr. Joseph I. Linde, F.A.C.P., New Haven, Conn., was recently elected President of the Connecticut Tuberculosis Association.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., spoke on "The Care and Feeding of Executives" at a meeting of the Chicago Conference on the Health of Industrial Workers, January 13, 1943.

Dr. George M. Decherd, Jr., F.A.C.P., has been named Associate Professor and Clinical Biochemist at the John Sealy Hospital of the University of Texas Medical Branch, Galveston.

Dr. Tinsley R. Harrison, F.A.C.P., Professor of Medicine at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., delivered the Alpha Omega Alpha Lecture at the medical college on November 24, 1942. Dr. Harrison spoke on "Cardiac Dyspnea."

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., addressed a meeting of the Indianapolis Medical Society on "Bleeding Lesions of the Gastrointestinal Tract," November 24, 1942.

Dr. Hugh G. Jeter, F.A.C.P., Oklahoma City, Okla., recently spoke on "Paracentetic Fluid as an Aid in Diagnosis" at a meeting of the Sedgwick County Medical Society, Wichita, Kan.

The Harvard Medical School is sponsoring a course of public lectures on medical subjects. On January 3, Dr. George W. Thorn, F.A.C.P., Boston, Mass., delivered the first lecture on "The Role of the Endocrine Glands in Adaptation." On January 31, Dr. Maxwell Finland, F.A.C.P., Boston, spoke on "Common Colds and Their Complications" and on February 7, Alexander Marble, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, spoke on "The Care of Soldiers in an Army Hospital."

Dr. Fay A. LeFevre, F.A.C.P., Cleveland, Ohio, spoke on "Treatment of Coronary Heart Disease" at a "Victory Day Clinic" conducted by the staff of Mount Carmel Mercy Hospital, Detroit, Mich., on January 27, 1943.

On February 4, 1943, Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., President of the College, spoke on "The Contribution of the Physician in the Present Crisis" at a special mid-winter meeting of the Rhode Island Medical Society in Providence.

The meeting of the Medical Society of Milwaukee County held in Milwaukee, Wis., January 8, 1943, was devoted to an "information please" program on Therapeutics. Among those who participated were Dr. Edward H. Ryneerson, F.A.C.P., Rochester, Minn.; Dr. Ovid O. Meyer, F.A.C.P., Madison; Dr. Francis D. Murphy, F.A.C.P. and Dr. Theodore L. Squier, F.A.C.P., both of Milwaukee.

Dr. Julius H. Comroe, Sr., F.A.C.P., York, Pa., has the distinction of being the first Fellow of the College who has two sons who are also Fellows of the College, Dr. Bernard I. Comroe and Dr. Julius H. Comroe, Jr., both of Philadelphia.

The 39th Annual Congress on Medical Education and Licensure was held in Chicago, Ill., February 15-16, 1943. Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., spoke on "Medical Licensure and Public Health" and George F. Lull, F.A.C.P., Colonel, (MC), U. S. Army, Ross T. McIntire, F.A.C.P., Rear Admiral, (MC), U. S. Navy, The Surgeon General, and Dr. Thomas Parran, F.A.C.P., The Surgeon General, U. S. Public Health Service, discussed "Medicine and the War."

Dr. William H. Perkins, F.A.C.P., Dean of Jefferson Medical College, Philadelphia, Pa., recently received an honorary degree of Doctor of Science at the 156th commencement exercises of Franklin and Marshall College.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the commencement address.

Dr. Charles F. Gormly, F.A.C.P., President of the Rhode Island Medical Society and Physician-in-Chief of the Rhode Island Hospital, Providence, was honored by the Rhode Island Dental Society. On January 27, 1943, the Society presented its medal and scroll to Dr. Gormly for "distinguished service to the community and to the dental profession."

Burroughs Wellcome & Co., of Tuckahoe, N. Y., and Sharp & Dohme, of Philadelphia, Pa., both manufacturing chemists, have been presented with the Army-Navy "E" Award. These companies are engaged in the production of immense quantities of medicinal preparations for our armed forces all over the world.

At the presentation of the award to Sharp & Dohme, Comdr. Edward L. Bortz, F.A.C.P., made the presentation address on behalf of the Navy.

SPECIAL NOTICES

DUTIES OF U. S. CITIZENS DEFENSE CORPS IN GAS DEFENSE

A program for civilian protection against gas is being rapidly developed by the Medical Division of the Office of Civilian Defense. Courses have been presented for physicians selected from the faculties of medical schools to be trained as instructors in the medical aspects of chemical warfare. Arrangements are now being made for the presentation of courses by these instructors in their own medical schools.

Training for non-medical personnel is provided in Gas Specialist Courses which since early December have been presented monthly at War Department Civilian Protection Schools. These schools are located at Amherst College, Amherst, Massachusetts; Purdue University, Lafayette, Indiana; Loyola University, New Orleans; Occidental College, Los Angeles, California; Stanford University, Palo Alto, California, and the University of Washington, Seattle, Washington.

The Gas Protection Service of the U. S. Citizens Defense Corps has been organized as follows: The Medical Division of the Office of Civilian Defense has a Gas

Protection Section responsible for organization and training for gas defense. This section functions through the nine Civilian Defense Regions, which are coterminous with the Service Commands of the U. S. Army. Regional Gas Officers have been designated for several of the coastal Regions to supervise and assist the State Gas Consultants and the Senior Gas Officers of defense councils in the organization of State and local programs. The Senior Gas Officer trains Gas Reconnaissance Agents who serve in each zone of the city. These men are responsible for the identification of the agent, the collection of samples, the prevention of casualties, the delimiting of gassed areas, and for coöperation with the Emergency Medical Service, the Health Department and other agencies concerned in protection against gas.

Instructions to members of the U. S. Citizens Defense Corps on their duties in gas defense have been issued by the U. S. Office of Civilian Defense in Operations Letter No. 104 (Supplement 3 to Operations Letter No. 42), dated January 11.

The duties to be performed before, during and after gas attacks are outlined for the following individuals and groups: State Gas Consultant, Senior Gas Officer, Assistant Gas Officers, Gas Reconnaissance Agents, Laundry Officer, Commander of the Citizens Defense Corps, Incident Officer, Air Raid Wardens, Police Services, Fire Services, Emergency Medical Service, local Health Department, Public Works, Public Utilities, Transportation Services and Emergency Welfare Services.

For the Emergency Medical Service the duties are set forth as follows:

Duties before gas attack:

1. Plan with assistance of Senior Gas Officer for the establishment of gas cleansing stations for cleansing gassed patients with other injuries and for cleansing of civilian protection personnel. Each hospital of 150 beds or more should be provided with a cleansing station. Cleansing stations should be available in the ratio of one per 50,000 population and should be located at smaller hospitals or casualty stations where 150-bed hospitals are not available in this ratio.

2. Recruit, train, and assign personnel to gas cleansing stations for cleansing services.

3. Provide instruction, in coöperation with the Senior Gas Officer, for general public and civilian protection personnel in self-protection and self-cleansing (Operations Letter 46).

4. Provide for instruction of physicians in diagnosis and treatment of chemical casualties.

5. Assist hospitals in planning for handling of gas casualties.

6. Assure adequate distribution of protective clothing and gas masks and other protective equipment to members of mobile medical teams and train personnel in their use.

7. Make provision for training drivers of ambulances and sitting case cars in protection of their equipment against liquid-gas contamination; inform them of arrangements for vehicle decontamination by Emergency Public Works Service.

8. Arrange for the protection from contamination of the equipment used to transport contaminated casualties insofar as it is possible.

Duties during gas attack:

1. Upon advice of the Senior Gas Officer and under the orders of the Commander, man the gas cleansing stations.

2. Advise other services of the U. S. Citizens Defense Corps in regard to first-aid cleansing of their personnel.

3. Assign a mobile medical team to gas cleansing stations for first aid.

Duties after gas attack:

1. Evaluate the effectiveness of the cleansing procedures which have been used.
2. Provide follow-up treatment of patients.
3. Prepare inventory of protective equipment available for use in future attacks and obtain additional equipment as necessary.
4. Cleanse bodies of the dead to facilitate identification.

Important functions assigned to the health department in the local program of gas defense are as follows:

Duties before gas attack:

1. Provide for analyses for war gases in samples of food and water. These tests may be performed in a local health department if laboratory facilities are adequate. In such case it is desirable to utilize the same laboratory facilities for the analysis for war gases of air and other materials. Where laboratory facilities other than those of the local health department are more suitable for use in the analysis of war gases, arrangements should be made by the local health department for the analysis of samples of water and food.

2. Advise the Senior Gas Officer regarding the nature of instructions to the public concerning precautions to be taken in the event of water-supply contamination. Such instructions are to be promulgated by the health officer.

3. Coöperate with waterworks officials in planning for the protection and decontamination of the water supply.

Duties during gas attack:

1. Collect samples of food and water for laboratory analysis if contamination is suspected.

2. Inform the public regarding contamination of food and water supplies, including recommendations in regard to self-protection.

Duties after gas attack:

1. Decontaminate, destroy, or otherwise provide for the handling and disposal of contaminated food supplies.

2. Assist the waterworks in the treatment of contaminated water supplies.

3. Advise the Senior Gas Officer in regard to the safety of the public water and food supplies and inform the public regarding contamination of such supplies, and methods of dealing with it.

4. Obtain reports of analyses of samples of water or food and take appropriate action. Save specimens of contaminated water and food for transmission whenever necessary to a Chemical Warfare Service or other laboratory, by the Senior Gas Officer.

Gas masks are now being distributed to the personnel of the protective services. As a guide to local distribution and care of masks, the U. S. Office of Civilian Defense issued Operations Letter No. 106, January 20.

It is recommended that masks be distributed among the protective services of the U. S. Citizens Defense Corps in approximately the following proportions: Staff, 12.5 per cent; Fire Service, 10.5; Police Service, 18.5; Air Raid Warden Service, 30; Rescue Service, 1.5; Medical Service, 12.5; Public Works, 9; and Public Utilities, 5.5.

Masks should be kept at the post where the protective personnel will assemble during drills or enemy action, not carried by them during their daily activities, the Operations Letter advises. It is recommended also that about 20 per cent of the masks

allocated to each service be stored as a reserve. It is important that the reserves be decentralized as a safeguard against destruction by fire or bombing and also to permit rapid distribution in case of an emergency.

The directive points out that since valuable and critical materials are used in the manufacture of gas masks, the utmost care must be exercised in the handling, distribution and storage. No person should receive a mask until he has been trained in its use and care, including proper storage, it is advised.

Storage must be in a cool, dry place and masks should be kept from contact with sunlight, oils and corrosive liquids and vapors. After use, masks should not be worn by another individual without proper sterilization, instructions for which are given in the OCD publication "Protection Against Gas."

Repair of masks is not to be attempted locally except in case of extreme necessity, the Operations Letter states. Broken and defective masks or those with exhausted canisters should be collected by the local Property Officer and returned to OCD Supply Depots for repair and replacement.

THE RÔLE OF THE MEDICAL DEPT. IN COMBAT BY MAJOR NATHAN H. COHEN, M.A.C.

The primary mission of the Medical Department is the conservation and maintenance of the fighting strength of the forces in the field, and the care and treatment of the sick and injured in all the military forces. The peacetime mission of the Medical service is accomplished without much difficulty due to the fact that the medical establishments are fixed and located that all requiring medical aid may receive it instantly. The accomplishment of the wartime mission of the Medical Department is an entirely different matter which presents many great difficulties.

It is an established fact that the treatment rendered a soldier the first few hours after he is wounded, may mean the difference between complete and rapid recovery or death. Consequently, one of the most vital considerations of medical tactics is the beginning of treatment to the wounded as promptly as possible. Due to the rapidity of movement of troops in modern warfare, getting medical personnel to the wounded and evacuating the wounded to medical establishments presents a vast and complicated problem. It must be borne in mind that the primary mission of the fighting forces is the defeat of the enemy. All other considerations are secondary. Therefore the combat forces are necessarily given priority in the use of roads, terrain and the transportation of men and supplies. The Medical Department is allowed the use of only those roads and that ground which will not interfere with the movement of the combat forces. The evacuation of casualties is thus carried out with extreme difficulties as it is made against the forward movement of troops and supplies.

Each military unit has its own medical detachment which accompanies it into the field of combat and sets up its medical establishment. Some of these installations, such as the battalion aid station are located as far forward as 200 yards from the front line so that casualties may receive almost instant attention. These establishments operate while subject to the same dangers and hardships as the combat units. The Red Cross symbol no longer offers any protection against enemy attack.

Each medical unit is but a part of the fighting unit to which it is attached. Unless it understands how its team is going to play it cannot take part in the game intelligently. It is therefore necessary that medical department officers in the field are not only well versed in their professional qualifications but that they also understand the tactics and technic of the branch of the service to which they are attached. They must also be skilled in the art of military map reading and in the solution of combat

problems. Unless the tactical situation is thoroughly understood, efficient medical service cannot be rendered. With such a knowledge the commander of a medical unit can estimate where the bulk of casualties will occur, how many medical installations should be established and when and where to place them to get maximum protection from enemy fire. He can then intelligently prepare the combat orders for his unit.

It is thus seen that the Medical Department officer of today must not only be a doctor, dentist, veterinarian, etc., but also a soldier well versed in the tactics and technic of the Infantry, Cavalry, Engineers, Artillery, Air Forces and all the other branches of the service. With such a background our Medical Department may be depended upon to render the finest and most efficient medical service possible.

DALLAS SOUTHERN CLINICAL SOCIETY

The Fifteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society, which was to be held on March 22 to 25 (inc.), 1943, has been cancelled because of the war emergency.

The Hermann M. Biggs Memorial Lecture which is held annually in Hosack Hall at The New York Academy of Medicine under the auspices of the Committee on Public Health Relations will be delivered this year on Thursday, April 1, at 8:30 p.m. by

Lt. Col. Paul F. Russell,
Medical Department, Army of United States,
Chief, Tropical Disease and Malaria Control Section,
Division of Preventive Medicine,
Office of The Surgeon General.

The subject of the lecture will be "Malaria and Its Influence on World Health."
This lecture is open to the general public.

OBITUARIES

DR. LEO RICEN

Dr. Leo Ricen, an Associate of the College, died in Portland, Ore., on September 8, 1942.

Dr. Ricen was born in Odessa, Russia, in 1872. He received his B.S. degree from the Imperial University of Kazan, Kazan, Russia, and in 1901 received his M.D. degree from the University of Oregon Medical School. During 1911 and 1912 Dr. Ricen undertook postgraduate work in bacteriology at the Pasteur Institute and the University of Paris, Paris, France. During the latter part of 1912 he undertook additional work in x-ray diagnosis and gastro-enterology at the University of Vienna. He returned to the University of Vienna for additional postgraduate work in 1928.

Dr. Ricen was an instructor in the Department of Medicine at the University of Oregon Medical School from 1915 to 1920. He was also a member of the attending staff at the Emanuel Hospital from 1920 to shortly before his death. He was a member of the American Medical Association and its affiliated local, the Multnomah County Medical Society. He was also a member of the Northwest Medical Association and the Association for the Study of Internal Secretions. He has been an Associate of the American College of Physicians since 1924.

Dr. Ricen was a man of broad culture and deep intellectual attainments. The field of medicine was just one of the many subjects in which he was learned. His library of Russian literature was one of the best on the Coast. He was at home in the classics, in poetry and especially in world history. He was also a painter of considerable talent and he left some creditable art works to members of his family and friends. He was a lover of music and philosophy. Although a modest man in company, he was a brilliant conversationalist. Those who knew him valued his friendship and mourned greatly when he passed away.

HOMER P. RUSH, M.D., F.A.C.P.,
Governor for Oregon

DR. GEORGE MEADE SETTLE

On September 15, 1942, Dr. George Meade Settle, F.A.C.P., Baltimore, Md., died at the age of 62 years, after a six weeks' illness, following a coronary thrombosis. In his passing, the College has lost a staunch supporter and one who was untiring in his efforts and interests to increase the College activities in Baltimore.

Dr. George Meade Settle was born in Leeds, Md., September 9, 1880. He attended Friends School in Wilmington, Del., and received his A.B. degree in 1902 and his M.D. degree in 1905 at the University of Pennsylvania School of Medicine. He was Assistant in Neurology, 1909-1911; Instructor in Neurology, 1912-1914; Associate in Neurology, 1914-1916; Instructor in Physical Diagnosis, 1912-1914; and Associate Professor of

Neurology and Clinical Medicine, 1916 to date, at the University of Maryland School of Medicine. For many years he was Visiting Neurologist, Maryland General and University Hospitals and Hospital for Women; Consulting Physician, Harford Memorial Hospital, Havre de Grace, Md. He was a member of the Baltimore City Medical Society, Medical and Chirurgical Faculty of Maryland, and the American Medical Association; and was a Fellow of the American College of Physicians since 1927, and a Life Member of the College since 1937.

To know Dr. Settle was to love him. To have been a friend of his was something to be cherished. Those of us here who knew him so well know that in his passing he had no regrets, but his patients and many friends feel his death very keenly.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

DR. ELMER BURKITT FREEMAN

On December 23, 1942, the Maryland Chapter of the College sustained another loss in the death of Dr. Elmer Burkitt Freeman, Baltimore, who had been a Fellow of the College since 1929.

Dr. Elmer Burkitt Freeman was born at Mattoon, Ill., February 5, 1875, and died at Baltimore, December 23, 1942. He received his B.S. degree from Austin College in 1896 and his M.D. degree from the Baltimore Medical College in 1900. He was Instructor in Clinical Medicine, Baltimore Medical College, 1901-1904; Associate Professor of Clinical Medicine, Baltimore Medical College, 1904-1910; Associate Professor of Clinical Medicine, University of Maryland School of Medicine, 1913-1914; Professor of Therapeutics, Baltimore Medical College, 1910-1914; Assistant in Clinical Medicine, Johns Hopkins University School of Medicine, 1916-1922; Instructor in Clinical Medicine, Johns Hopkins University School of Medicine, 1922-1929; Associate in Clinical Medicine, Johns Hopkins University School of Medicine, 1929 to date. For many years Dr. Freeman was Physician-in-Chief, Maryland General Hospital; Assistant Visiting Physician and Dispensary Physician, Gastro-intestinal Department, Johns Hopkins Hospital; Visiting Physician, Church Home and Infirmary; Gastro-enterologist, St. Agnes Hospital; Attending Gastro-enterologist, Bon Secours Hospital, and a member of the active staff, Union Memorial Hospital. He was a Diplomate of the American Board of Internal Medicine and the author of many published papers. Dr. Freeman was a member of the American Gastro-enterological Association, the American Radiological Association, the Southern Medical Association, the Medical and Chirurgical Faculty of Maryland, and the Baltimore City Medical Society. He was a Fellow of the American Medical Association and a Fellow of the American College of Physicians. Dr. Freeman served during the first World War on the local Advisory Medical Board and was serving on Local Induction Board No. 6 at the time of his death.

The untimely death of Dr. Freeman was a severe shock to his many friends and patients. Dr. Freeman was a loyal supporter of the College and of the Maryland Chapter and never failed to do his part in making any of our functions a great success. His passing is a great loss to the teaching institutions of the city, as well as to his friends and medical associates.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

DR. HARRY BOND WILMER

Dr. Harry Bond Wilmer, noted allergist, died very suddenly at his home on January 16, 1943. Dr. Wilmer was an outstanding physician in Philadelphia and his work in the special field of allergy had gained for him a renowned position in American medicine.

He was born May 12, 1884, in Baltimore, Maryland, and attended St. John's College and the United States Naval Academy at Annapolis. He received his medical degree from the University of Pennsylvania School of Medicine in 1906. During the last World War he served as a Captain in the United States Army at Base Hospital No. 10.

For many years Dr. Wilmer was Director of the Allergy Department at Abington Memorial Hospital, and was also associated with the Allergy Department at the Graduate Hospital in Philadelphia. In addition to his other duties at Abington he held the position of Medical Director for several years.

Dr. Wilmer was a teacher as well as a practitioner of medicine. He was an Associate Professor at the University of Pennsylvania Graduate School of Medicine.

Medical activities included his membership in the American Allergic Association, having been former President of that group and the American Clinical and Climatological Society. He was a Fellow of The American College of Physicians, and in the past, has served on various committees. He was also a Diplomate of the American Board of Internal Medicine.

Sports commanded his enthusiasm in the form of yachting at which he was an expert. He was former Commodore of the Corinthian Yacht Club and the Chester River Yacht and County Club.

Dr. Harry Wilmer was loved, admired and deeply respected by his many friends and associates in and about Philadelphia. He particularly endeared himself to the membership of the College from this area by becoming intimately identified with the entertainment work associated with many regional meetings that were held here. His brilliant mind, keen sense of humor and wonderful personality have indelibly imprinted themselves in the minds and hearts of his many friends, and he will forever be remembered by them. It is indeed with humble thought and deep sorrow that we write of the passing of Dr. Harry B. Wilmer.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

REPORT AND ABSTRACT, MINUTES OF THE BOARD OF REGENTS

DECEMBER 13, 1942

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at Philadelphia, December 13, 1942, with President James E. Paullin presiding, with Mr. E. R. Loveland acting as Secretary, and with sixteen members of the Board and the Chairman of the Advisory Committee on Postgraduate Courses, Dr. E. L. Bortz, in attendance.

After reading of the Minutes of the preceding meeting and the presentation of various communications, Dr. Charles F. Tenney, who acted as a representative of the College at a meeting of the American Physiotherapy Association in New York during August, 1942, made a comprehensive report. He reported that Dr. Philip D. Wilson is Chairman of a permanent Council formed by the American Physiotherapy Association to aid in the rehabilitation of war casualties. The Council consists of seven members. It has under consideration the presentation of a bill before Congress which may have the President's support. The Council may request the organizations which were represented at the August meeting, such as the American College of Physicians, the American College of Surgeons, et al., to make a small donation to cover secretarial and other expenses. It is provided in the bill that the American Physiotherapy Association stands ready to give its services, under the direction of qualified physicians, to help rehabilitate the casualties of the present war, as well as veterans of the past war, and, in addition, other casualties such as may properly come under Government supervision.

President Paullin, for matter of record in the Minutes, reported a meeting of several Officers and Regents of the College at Philadelphia, with the subsequent approval of the Board of Regents, providing for the cancellation of the 1943 Annual Session and of future Annual Sessions for the duration of the war. A resolution was adopted approving the action of the Committee and of the mail vote taken among the Regents.

The Secretary, Mr. Loveland, presented for clarification by the Regents the following provision adopted by the Board at its preceding meeting: "The initiation fee of members serving with the armed forces and completely detached from private practice, at time of election, shall be reduced to \$10.00, this regulation becoming effective as of January 1, 1942." After discussion, by resolution formally adopted, the regulation was altered to read: ". . . at time of election, *or within two months therefrom. . .*"

The Secretary General, Dr. George Morris Piersol, reported the deaths of thirty-one Fellows and seven Associates since the preceding meeting of the Board, and the names were spread upon the Minutes. Dr. Piersol also reported four additional life members since the last meeting of the Board, making a total of 187, of whom 21 are deceased, leaving 166.

President Paullin filed a final report on the evaluation of physicians, which the College undertook in order to assist the Surgeons General of the Army and Navy in placing physicians who volunteered for military service in that type of work for which they would be best suited. This work was made possible through the very enthusiastic and hearty coöperation of a large group of physicians, Governors, Regents and members of the American College of Physicians, and other individuals. Altogether there were 369 helping in this work. Dr. Paullin's office completely evaluated and furnished information concerning 11,383 internists and 5050 pediatricians. In addition, the National Research Council requested that the general practitioners be evaluated, of whom there were about 60,000. Of these 38,000 were investigated, but the

work was discontinued because of the difficulty in obtaining adequate information. For the most part, these general practitioners were little known, were located in smaller communities, and it was found extremely difficult to appraise their qualifications. Dr. Paullin's office further evaluated 1,750 members of the Medical Reserve Corps so that, all told, this Committee collected definite information of a trustworthy nature concerning 56,184 doctors, and this information has been placed at the disposal of the Surgeons General of the Army and Navy.

Dr. Paullin further pointed out that all members of the College, Fellows and Associates, were evaluated. Data were recorded on cards, and the most complete professional detail on at least four thousand physicians was assembled that has been possible in any other organization in the United States. This information has been used in the offices of the Surgeons General, and, as a result, members of the College in particular have been assigned, in the majority of cases, to work which they can best do.

By resolution, regularly adopted, the Regents expressed their appreciation to Dr. Paullin for the enormous amount of valuable work accomplished, and, since the work is completed, discharged his Committee.

President Paullin recommended that the College should have a committee that will be able to function in an advisory capacity with some agency of the Surgeons General's offices of the Army, Navy and Public Health Service and the Office of Procurement and Assignment. He felt it necessary for the College not only to plan for the medical future but to have a committee that will be looking to post-war planning not only as it concerns members of the College but the profession as a whole.

Dr. George Morris Piersol, Chairman of the Committee on Credentials, distributed to the Board a mimeographed outline of all candidates that had been reviewed by that Committee on the preceding day. Of 193 candidates for Fellowship, 147 were recommended for election, 11 were recommended for election first to Associateship, 25 were deferred for further credentials, and 10 were rejected. Of 181 candidates for Associateship, 140 were recommended for election, 21 were deferred for further credentials and investigation, and 20 were rejected. (The list of candidates elected to Fellowship and to Associateship was published in the January, 1943, issue of this journal.)

On recommendation of the Credentials Committee, a resolution was adopted reinstating Major Rudolph A. Kocher, MRC, U. S. A., to Associateship. The application of a candidate for reinstatement as a Fellow was not approved because of lack of support by other Fellows in his community.

In accordance with provisions of the By-laws, 6 Associates were dropped from the roster because their five-year maximum term had expired without their presenting the necessary credentials for Fellowship.

The Executive Secretary, Mr. Loveland, made the following report:

"During the past year we published a Supplement to the 1941 Directory. The present membership, exclusive of today's election, consists of:

4	Masters
3,697	Fellows
1,109	Associates
<u>4,810</u>	Total

There are, at this date, 1,122 members serving in the Armed Forces. The average age of all members, Fellows and Associates combined, of the College is 49 years.

"We have refunded in dues to members serving in the Armed Forces over \$7,000.00, and we have given credit additionally of \$1,100.00. I predict that in 1943 the waiver of dues will cost us about \$15,000.00, and the reduction in Initiation Fees \$8,000.00.

"We have not had a resignation since the last meeting of the Board of Regents. This, out of a membership of over 4,800, I consider a record.

"We have had an increase of over 300 in the circulation of the 'ANNALS' during the past year, but we may anticipate a considerable shrinkage in the coming year, because the 'ANNALS' will not be furnished free to dues-waived members. We are attempting to offset this shrinkage by promoting subscriptions among non-members. The 'ANNALS,' however, has been placed on the approved and official lists of the Offices of the Surgeons General, and, as a result thereof, we have received numerous new subscriptions for Navy and Army hospitals.

"I wish to report further that my office is concentrating on an effort to build up income from additional advertising in the journal. With the cancellation of our Annual Sessions, manufacturers and publishers can no longer exhibit before the College; we are emphasizing the importance of their maintaining their contacts with our membership through increasing their advertising in our journal.

"I report also to the Regents that Dr. Samuel M. Poindexter, of Boise, has been appointed by the Executive Committee as the Acting Governor for the State of Idaho, serving in the place of Dr. Charles Henry Sprague.

"Dr. Thomas M. McMillan, of Philadelphia, has been elected Acting Governor for Eastern Pennsylvania, but he has not taken office due to the fact that Commander Edward L. Bortz is still located in Philadelphia and continues to serve.

"Dr. Patrick L. Ledwidge, of Detroit, has been elected Acting Governor for Michigan in the place of Dr. Douglas Donald, who is in the Service.

"Dr. Edward H. Rynearson, of Rochester, Minn., has been elected Acting Governor for Minnesota, in the place of Dr. Edgar V. Allen, who is in the Service.

"Dr. J. Edwin Wood, Jr., of University, Va., has been elected Acting Governor for Virginia, in the place of Dr. Walter B. Martin, who is in the Service.

"Dr. Charles F. Tenney, New York City, has been appointed, under provisions of the By-Laws, as a Regent of the College, to serve until the next regular election, because of a vacancy occurring through oversight of the Nominating Committee at the St. Paul Session when Dr. Irons' place on the Board became vacated due to his elevation to the post of President-Elect."

Dr. David P. Barr reported for the Committee on Public Relations. In accordance with recommendations of the Committee, resolutions were adopted providing for the waiver of the dues of five Fellows, due to illness, until their recovery and resumption of practice.

Dr. Barr reported also that two medical societies had invited the American College of Physicians to organize joint meetings with them during 1943. These invitations had been considered by the Committee and since it was thought that they may be only two of several which may be received in the future, the Committee offered the following recommendation in the form of a resolution: "It is the opinion of the Committee on Public Relations that Regional Meetings of the College are the responsibility of the College and its Governors and that the programs, together with such other activities as postgraduate seminars, examinations, etc., should be supervised by local representatives and under the direct control of the Program Committee of the College." Such Regional Meetings are, of course, open to all members of the medical profession in good standing in such communities." A motion for the approval of this resolution was made, seconded and carried.

On behalf of the Committee on Public Relations, Dr. Barr presented several additional communications, including one from Captain David W. Exley, expressing the feeling that Fellows of the College should be utilizing more than they are permitted, their special training as internists in the Army. President Paullin reported that

measures have been undertaken along this line and that no further action is required at this time. Perhaps fifteen complaints of this character have come through the College and these have been cleared through the Office of the Surgeon General. That office has always shown a ready willingness to rectify any mistakes. It was revealed that out of the 1,122 College members on active duty, reports of 15 or 20 maladjustments had been received, which is a small percentage and should be looked upon with considerable credit to the Office of the Surgeon General.

By resolution, the report of the Committee on Public Relations as a whole was adopted and the Secretary instructed to communicate with the two societies from whom invitations had been received for joint meetings.

Dr. Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, made the following report:

"This year the Committee arranged for three Courses, and you have in your hands the galley proof of the details of the curricula. Dr. Robert Cooke was unable this year to repeat his course in Allergy. Another course in general medical science planned in Philadelphia had to be abandoned because suitable arrangements could not be completed.

"The three Courses scheduled are all in Internal Medicine—No. 1 at the University of Minnesota, under Dr. Cecil Watson, and with the coöperation of Dr. William A. O'Brien, Director of Postgraduate Education; No. 2 at the Mayo Clinic under Dr. E. H. Rynearson; No. 3 at Boston University under Dr. Chester Keefer. There has been a modest and wise condensation of the work of our Committee, in the face of the present altered conditions. With 25% of our membership in the Armed Forces today, it is impossible to estimate the registration. The Committee is hopeful that there will be a generous response. There has been a suggestion that the Surgeons General may assign men from their respective Services to take these courses. No fee will be required from any registrant from the Army or Navy. Men who are not members of the College, but are of College material and aspire to membership, will presumably, with your permission, be permitted to enroll in these courses upon payment of the usual fee.

"Another series of three sessions of 'Postgraduate Nights' was held in Philadelphia at the Naval Hospital this autumn. The program was an excellent one, arranged by Dr. Thomas M. McMillan, and was widely publicized in this area, not only at the Naval Hospital, but at the Army Hospital at Camp Dix. The auditorium was practically filled each evening, and the men were most enthusiastic about the program. Terminating the 'Postgraduate Nights' program, the annual Eastern Pennsylvania Round-Up was held in Philadelphia, culminating in a very spirited and enjoyable dinner meeting at the Union League, at which the College was privileged to have as its chief dinner speaker Admiral Ross T. McIntire, Surgeon General of the Navy. The whole program was so well received by officials of the Army and Navy that a request has already been made for another series of 'Postgraduate Nights' in the spring.

"Governor LeRoy H. Sloan, of Northern Illinois, likewise organized a series of 'Postgraduate Nights' at Camp Grant and at the Great Lakes Naval Hospital, culminating in a Regional Meeting for Illinois, Indiana, Iowa, Michigan and Wisconsin at Chicago on November 21. Approximately two hundred medical officers were in attendance at each program of 'Postgraduate Nights,' with a large attendance at the Regional Meeting. Outstanding representatives from the Offices of the Surgeons General appeared on the program, including General C. C. Hillman, of the Army; General David N. W. Grant, Army Air Surgeon; and Captain Robert E. Duncan, of the Navy. It would have been a good opportunity at the evening dinner meeting for an official representative of the College to have explained in some detail the activities and objectives of the College. However,

the meeting was highly successful, as evidenced by additional requests for further 'Postgraduate Nights' programs at Camp Grant and at the Great Lakes Naval Hospital. A further extension of this program is at present being developed by Governor William B. Breed for the New England States. Additional requests are coming in from other hospitals and camps throughout the entire nation. We have not extended ourselves too widely. We have proceeded cautiously, offering the facilities and the splendid teaching personnel included within the membership of this College. I have received no adverse comment. On the other hand, there has been a steady and increasing pressure for more and more activity of this kind. Here is a magnificent opportunity for the College once more to demonstrate its leadership in the field of medical education, as far as Internal Medicine is concerned. There is also a demand for instruction in other fields, especially surgery. We have been thinking about a broader program—by establishing an organization by which surgery and other specialties would be brought into the setup. In consultation with your President, the following resolution has been prepared:

"WHEREAS there has been a definite need for the extension of postgraduate facilities to medical officers of the Armed Forces, as shown by the enthusiastic attendance and response on the part of all who have attended the 'Postgraduate Nights' and Regional Meetings which have been held by the American College of Physicians during the past year and increasing urgent demands for this type of teaching, and

"WHEREAS this need for advanced training is bound to become greater the longer the war lasts, and

"WHEREAS the American College of Physicians has personnel and facilities for the development of extension courses in the form of lectures, conferences, teaching ward rounds, seminars, 'Postgraduate Nights' and round table discussions, therefore

"BE IT RESOLVED that the American College of Physicians extend its activities in this field and join with the American Medical Association, through its Council on Scientific Assembly, and with the American College of Surgeons to make a study and draw up a complete plan, listing the available personnel and, where possible, the locations for instruction, subjects to be discussed and other pertinent matters, to the end that a continuous plan of advance instruction for all doctors in the Armed Forces be furnished.

"IT IS RECOMMENDED that the Finance Committee be requested by the Board of Regents to make available funds up to the sum of \$5,000.00, to be expended under the supervision of the Committee on Postgraduate Courses of the American College of Physicians toward the furtherance of this program.

"IT IS FURTHER RECOMMENDED that there be appointed a Committee with power to act, consisting of equal representation from the American College of Physicians, the American Medical Association and the American College of Surgeons to develop a program and put it into execution."

President Paullin remarked that such a comprehensive, well worked out program might be given some financial support from the Kellogg Foundation and perhaps from the Rockefeller Foundation in order to make available this type of instruction.

Dr. Henry R. Carstens, remarking upon this action, said, "I think this is a splendid idea. I attended the Regional Meeting in Chicago, and consider it one of the most delightful meetings I ever attended. Enthusiasm was great among the military attendants. There was a large delegation from Camp McCoy. The program went through with perfect precision. There was a galaxy of stars among the speakers, and every one was commenting on what a wonderful meeting it was. I hope this will be extended."

By motion, the above resolution was accepted and adopted.

By resolution, regularly adopted, Dr. Bortz' report as a whole was approved and his recommended resolution adopted.

Dr. Ernest E. Irons, Chairman of the Committee on Educational Policy, reported that Dr. Bortz' report had been formulated at a joint meeting of the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses. He added, in part: "I should like to comment that our inability to hold an Annual Session may be the best thing that has happened to the College, because it gives an opportunity for developing local Regional Meetings. The local interest of men in the College is being greatly facilitated. I believe the College work is being furthered more than it would be if we had only the Annual Session."

Dr. Francis G. Blake made the following report for the Committee on Fellowships and Awards:

"Since our St. Paul meeting, Dr. Joseph L. Lilienthal, Jr., who was awarded a fellowship to work at Vanderbilt, resigned on July first to enter the military service, and his resignation was accepted. The other two Research Fellows—Dr. James Hopper and Dr. Carl G. Heller—are now actively engaged in work, and as far as we know at present they expect to complete their fellowships this year.

"When it became clear that no Annual Session would be held this year, the membership of our Committee was canvassed by mail with respect to two matters: (1) whether any fellowships should be awarded for the coming year; (2) whether the John Phillips Memorial Award should be made this year. The Committee has voted unanimously that the College discontinue awarding Research Fellowships until after the War, and that since the annual meeting is cancelled, the John Phillips Memorial Award be withheld until such time that a meeting of the College will be held."

By individual motions, seconded and regularly carried, both recommendations of the Committee were adopted.

Dr. Ernest E. Irons, Chairman, reporting for the American Board of Internal Medicine, said that the number of applications for examination, contrary to their expectations, has increased. In October, 1942, there were 307 examinees from 24 cities. In addition, there were 87 examinees in the Armed Services who took the examination in 38 different military camps. The Board has approved such methods of giving written examinations and has received the most complete coöperation from the commanding officers in various camps with but one or two exceptions. The Board during the past year had certified 193 by examination, and 20 without examination. At the time of this meeting a total of 1,038 physicians had been certified by examination and approximately 1,800, from previous actions, without examination, making approximately 2,838 thus far certified by that Board.

Dr. Irons, on behalf of the Board, asked the advice and assistance of the Regents of the College with regard to problems arising from the termination of maximum terms of some members of the Board by July 1, 1943. Dr. Jonathan Meakins, now Deputy Director of the Canadian Medical Service, is forced to resign under the strenuous conditions of his work, and the Board has accepted that resignation regretfully. "Dr. Meakins has been a power for idealism and practical application, and the Board has gone on record in the recommendation of the recognition of his very able services." The terms of two other members will expire in June. The Board is reluctant to make changes in the present war times and is looking for a method of retaining the services of these two men for the duration of the war or until they can be replaced by suitable successors.

The Board considers it desirable to introduce into membership men of the age of 45 to 55; the situation has been canvassed, but such men are not available at present

for they all appear to be in the Armed Forces; hence the Board wants to retain Dr. Reginald Fitz and Dr. G. G. Richards if possible. It was pointed out that Dr. Fitz is an appointee of the American Medical Association and that Dr. Richards and Dr. Meakins are appointees of the College.

Continuing his report, Dr. Irons said that if there are no objections on the part of the Board of Regents, the American Board of Internal Medicine will proceed with its previous decision to reduce the examination fee from \$40.00 to \$30.00 as of January 1, 1943. There were two reasons why the Board had suggested a reduction: (1) to coöperate in spirit with the College, and (2) it did not wish to materially increase its funds.

The final matter presented by Dr. Irons referred to certain criticisms that had been raised in a meeting of the Board of Governors of the College at St. Paul. Among these had been a communication from the Buffalo district, giving the names of candidates involved in the general complaint. The Board had drawn up a complete report on the history of each case and a communication had been forwarded through the Executive Secretary of the College, as follows: "As has been indicated repeatedly, the Board desires at all times to be fair. It is customary in conducting examinations to have a Board member and a guest examiner form an examining team, so that at least two men, and if reëxamination is necessary, four men (two of them members of the Board and two guest examiners) render opinions on the qualifications of the candidate. In a few instances the reëxamination may be conducted by a Board member only, but this is not the rule. It is of interest to note that frequently the judgment of the guest examiners, chosen for their outstanding ability and standing in the city in which the examination is held, is more severe than that of the members of the Board. It should be unnecessary to say that the intent and, I believe, always the practice of members of the Board, is to be uniformly courteous. Candidates are frequently nervous and distraught and often require encouragement before the examination can proceed. Such candidates may well misinterpret what is said to them.

"One point is to be reiterated in regard to the written examination: The examination questions frequently include questions which have perhaps no immediate clinical application, and sometimes might be regarded as catch questions. A candidate is never failed by reason of failure to answer such question. Judgment is based on his handling of the question and his ability to reason out an answer. In general, it is planned to give an examination distinctly more difficult than that which would be given to fourth-year medical students.

"In spite of all efforts to make examinations of the Board searching and still fair, it is quite possible that errors may creep in. These the Board regrets. However, the candidate may repeat the examination. It frequently has happened that candidates, after having passed the reëxamination, have come to members of the Board and stated that they were very grateful for having been failed in their first examination, because they had now learned what real work and study is and have corrected their faults.

"Finally, with respect to the comments of the Board of Governors concerning the embarrassment which results from failure of men to pass the Board and thereby become eligible for Fellowship in the College: This would seem to be a question for the College to consider. The Board is not and cannot be concerned with qualifications of candidates aside from those expressed in their applications as to preparation, the opinions of physicians given as references, and their medical preparation as indicated by the written examination, by oral examination, and by their ability to handle patients and to arrive at accurate clinical diagnoses. Failure to pass the examination of the Board is no reflection on a candidate's moral or social status.

"The only object of the Board in carrying on its work is to establish and maintain standards of performance which will lead to a further improvement in scholarship

in American medicine. In carrying out this program, the Board fully recognizes its responsibility."

In answering inquiries concerning whether there has been a time limit or an age limit for certification without examination, Dr. Irons replied:

"When the Board was first organized, it was necessary to put a time limit on applications for certification without examination. It was set at July 1, 1937, and the candidates came under certain categories: Fellowship in the American College of Physicians, membership in two of the scientific internal medical societies of national scope, and a number of others; also men recommended by the Executive Committee of the Section on Medicine of the American Medical Association. There were other men in smaller communities, often not closely associated with educational institutions, men who had never been joiners. They didn't want to join, yet they were perfectly magnificent practitioners of medicine. We included them. Since that time there have turned up a great many men who now say they would like to be certified and feel a little hurt that something hadn't been done about it, yet we couldn't do anything unless we were asked. If a man is in one of these special categories and was at least forty years of age in 1937, he can yet be certified without examination, provided all requirements are in order. If he is now over forty, it doesn't follow that he can be certified without examination, for he was only thirty-five in 1937. We are not going back of the rule, but we are just trying to correct omissions."

Motion was made to accept Dr. Irons' report, seconded and carried.

LUNCHEON RECESS

The afternoon session was called to order by President Paullin, who asked for the report from the Committee on the ANNALS OF INTERNAL MEDICINE by Dr. Reginald Fitz, acting in the absence of Chairman Palmer. The Committee reported that at present 2,400 pages per year of scientific matter are authorized by the Board. Owing to the large number of members in the Service who had their dues remitted, thereby reducing the income, and who do not receive the ANNALS, and also the probability of reduction in the receipt of suitable material, the Committee considered the desirability of reducing the number of pages per year. The Editor had reported enough material on hand for at least eight months. Because the ANNALS has an enviable position in the field of medical literature, the Committee believes nothing should be done to jeopardize this position, but at the discretion of the Editor some reduction may be made, consistent with maintaining the journal's high standing. The Committee approved the efforts being made by the Executive Secretary to increase the income by increasing advertisements moderately and by promoting the circulation among non-members. The Committee further recommended that the Editor review the programs of "Postgraduate Nights" and Regional Meetings for material suitable for the journal; also that the Board of Regents be requested to be on the lookout for original work suitable for publication in the ANNALS; that the ANNALS be offered to the men in Service at cost (\$6.00); and finally, the Committee expressed its appreciation to the Acting Editor, Dr. Paul W. Clough, for the excellent manner in which he had conducted the ANNALS since Editor Pincoffs entered active service.

On motion, seconded and regularly carried, the report of the Committee was accepted.

Dr. Paul W. Clough, Acting Editor, reported briefly, saying that up to that time he had received a very satisfactory number of articles and that he had 80 main articles and about 50 case histories, which had already been accepted for publication. This would be enough for eight or ten months, but at that time some marked dropping off in articles submitted is anticipated.

Dr. William B. Breed, reporting for the Board of Governors, reported as follows: "I would like to transmit an impression that I get from the Governors about these Regional Meetings. On November 9, upon return from Philadelphia after an extraordinarily successful meeting here, I wrote a letter to each Governor, pointing out the decision of that conference that we held concerning the discontinuance of the Annual Session, and asked the Governors to go into individual executive sessions to see what they may have to suggest by way of Regional Meetings in the various sections. I urgently requested that a group of Governors combine in certain sections to organize Regional Meetings. We shall hold a Regional Meeting in New England the first week in February, and cordially invite all of you to come. We expect to have Admiral McIntire, Brigadier General Grant, President Paullin, Secretary-General Piersol and other high lights of the College present. From the Governors I get the impression that while they are enthusiastic about doing something they are in doubt as to what regions should be organized. I would suggest that the Executive Secretary, Mr. Loveland, and the Committee on Postgraduate Courses and I try to decide on regions that seem appropriate and inform these Governors concerning a suggested organization; then we can say to the Governors, 'This is your region. You may not be able to have a Regional Meeting, but you belong in this setup when the time comes.'"

On inquiry from Dr. A. C. Griffith as to what part the central office plays in the conduct of Regional Meetings, the Secretary, Mr. Loveland, reported that his office prints and distributes the programs and performs every other service practically except the appointment of committees and the making up of the program itself.

Dr. O. H. Perry Pepper recommended that the Surgeon General of both the Army and Navy be invited to Regional Meetings.

Dr. Pepper, as Chairman of the Committee on Finance, reported as follows:

"1. The Committee recommends the use of the First National Bank of Philadelphia as one of the depositories of the College.

"2. The College has waived the dues of members in Service and has reduced the initiation fees to members in Service at an approximate cost for 1943 of \$23,000. In conversation with the American Board of Internal Medicine, it has been suggested that that Board reduce its fee from \$50.00 to \$40.00 and the College reduce its initiation fee from \$80.00 to \$65.00. The American Board has taken this action. The Executive Secretary estimates that the proposed reduction by the College would reduce our income for 1943 by \$2,850. The Finance Committee recommends that the College shall not make the proposed reduction in initiation fees, as it will apply only to members not in Service, most of whom are receiving higher professional incomes than usual because of increased work and increased ability of patients to pay.

"3. The Committee reports the following figures:

a. A year ago the surplus for 1942 was estimated at \$30,000. The actual surplus has proved to be \$26,515, a falling off of only \$3,485.

b. The 1942 income has fallen short by an estimated \$2,355.59. The 1942 expenses were \$5,057.86 less than the budget.

c. The income from investments for 1942 was approximately \$7,400, with trading profits of \$735.83, or a total of \$8,135.83.

"4. The Committee is informed that the total anticipated income of the College for 1943 will be \$82,410. The Committee recommends the adoption of the proposed budgets to a total of \$77,025, leaving an anticipated balance of \$5,385. In addition, the Committee recommends certain small additions to the proposed budget totalling \$1,215.

"5. (Thereafter the Committee's report delineated the distribution of this \$1,215 among various minor accounts, including certain adjustments in salaries, etc.)

"6. The two existing research fellows will receive in 1943 a total of \$2,100 if they are not called to active service. The proposed budget contains no item for additional fellowships.

"7. The proposed budget contains no items for the John Phillips Memorial Award, although a medal could be awarded at trifling cost. The main expense is usually that of travelling.

.....
 "12. In the 1942 budget the sum of \$2,500 was reserved for a new edition of the Directory and in the 1943 budget an additional sum of \$3,000 for this purpose appears. The Committee recommends that no new edition of the Directory be published in 1943, but that these sums continue to be reserved toward the publication of a large post-war edition, containing the war record of every member.

"13. In view of the omission of the Annual Session, a stimulation of Regional Meetings seems proper, and the budget contains an item of \$2,000 for this purpose. The Committee recommends an addition of \$500 to this sum. The Committee also recommends that the Regents set a maximum to the amount to be contributed by the College to any one Regional Meeting. At present some of these meetings have cost the College over \$500.00. The Committee recommends a maximum of \$250.00.

"14. The Committee recommends the acceptance of the sales and purchases of securities suggested by Drexel & Company, its financial advisers. (Thereafter followed the specific list of securities to be purchased or sold.) The Committee recommends that any residue be invested in U. S. Savings Bonds.

"15. The College has some \$27,000 in cash, of which some \$3,000 is in Canada. The Committee recommends that none of this cash be invested at present.

"16. The Committee expresses its confidence and satisfaction with the management of the affairs of the College by the Executive Secretary, the Treasurer, and Drexel & Company."

Individual motions by item of the Finance Committee's report were carried, approving each recommendation. Copies of the operating statements for 1942 and the budgets for 1943 were distributed, preceding the report, to each member of the Board.

On motion by Dr. Palmer, seconded and carried, it was provided that the \$5,000 previously set aside for the Directory reserve fund be diverted and appropriated for postgraduate education in military circles for 1943.

On motion by Dr. Palmer, seconded by Dr. Irons and regularly carried, it was provided that the recommendations of the Advisory Committee on Educational Policy and of the Committee on Postgraduate Courses, earlier presented in this meeting, be accepted and the program put into effect.

There followed a long discussion of the conduct of Regional Meetings, especially with regard to expenses therewith connected. It was brought out that the maximum deficit of any Regional Meeting that shall be made up by the College shall not exceed \$250.00. This does not include travelling expenses of the President, because he has a separate budget, but it does include all other travelling expenses, the cost of printing the program, postage, etc. No charge is made for services performed by the Executive Offices. Social functions at Regional Meetings should be arranged so that they will carry themselves. Generally speaking, there need not be too many invited guest speakers from long distances, but rather authorities from the States represented should be placed on the program.

Dr. William D. Stroud, Treasurer, gave the following report:

"The income of the College for 1942, with estimations for the month of December, will be approximately \$115,000.00; \$2,300.00 less than estimated. The gross expenditures for 1942, also with estimations for December, will be approximately \$82,000.00, leaving a surplus of about \$26,500.00. The College operated approximately \$5,000.00 below its budget.

"The book value, or purchase price, of its security holdings is:

Endowment Fund	\$136,174.32
General Fund	116,521.14
	<hr/>
	\$252,695.46

"The combined present cash value (that is, Endowment Fund and General Fund) of these securities is \$269,592.00.

"The College employs the same competent firm of Investment Counselors at the relatively small cost of about \$400.00 per annum, and receives frequent surveys of its security holdings, which are reviewed periodically by the Finance Committee of the College.

"To December 8, 1942, we have refunded in dues a total of \$7,244.00. It is estimated that the waiver of dues to Service members during 1943 will amount to approximately \$15,000.00, and the reduction in Initiation Fees to Service members to approximately \$8,000.00. This means a reduction in our income for 1943 of approximately \$23,000.00.

"We believe the financial condition of the College sound and satisfactory. The accounts, as usual, will be audited by a certified public accountant at the end of the year, and his statements published in the 'ANNALS.'"

By motion, seconded and regularly carried, the Treasurer's report was accepted. President Paullin introduced the subject of the election of Officers, Regents, and Governors, as well as members of the American Board of Internal Medicine during the war emergency. The Secretary reported that the Constitution and By-Laws make no provision for the election of Officers, Regents or Governors except for interim appointments in the place of those who may die or resign, except at the Annual Business Meeting of the College. He said it is not probable that an Annual Business Meeting can be held when there is no Annual Session, and the inference would be that the present Officers, Regents, and Governors should serve for the duration of the War, until the next regular election.

There followed an extended discussion. Dr. O. H. Perry Pepper expressed himself as a believer in bringing new members to the Board and resorting to any legal means possible to bring that about. President Paullin, while expressing a willingness to do whatever the Board of Regents desired, indicated his desire to be relieved as President because of a heavy burden of other duties which has fallen upon him. However, he expressed his willingness to carry on if the Board insisted.

The possibility of calling an Annual Business Meeting at the College Headquarters in Philadelphia in April was fully discussed, but the majority felt that few, if any, members of the College would attend such a meeting, and this would subject the Officers and Regents to certain criticism, for, in effect, they would be conducting the elections. The consensus in the end was that the Board had no authority to act, that the Constitution and By-Laws make no specific provisions, and since the Annual Meeting of the College has been cancelled, an act approved by the majority of members at large, the present Officers, Regents, and Governors would continue to serve until the next regular election. It was pointed out further that in most other associations

it is probable that the officers and directing bodies will be "frozen" in office in a like manner.

To fill the vacancy, July 1, caused by the resignation of Dr. J. C. Meakins as a representative of this College on the American Board of Internal Medicine, by resolution made by Dr. Griffith, seconded by Dr. Pepper and unanimously carried, Dr. James J. Waring of Denver was appointed.

President Paullin introduced a discussion with regard to arrangements for convocations for the induction of new members during the war. Secretary Loveland pointed out that two plans had been presented for consideration. First, that the College arrange regional convocations to be held at the larger Regional Meetings at which new members from those territories could be inducted. He pointed out that it is possible that no Regional Meetings will be conducted for some States. The second plan was that convocations be suspended for the period of the war, but that Fellowship certificates be issued immediately upon election and that at the end of the war a really great convocation for the induction of all these men be held. The latter plan he thought would cause a great impetus to the College and renew interest at that time.

A motion to accept the second suggestion was made by Dr. Cocke, seconded and unanimously carried.

A motion was made, seconded, and regularly carried, providing that there shall be a meeting of the Board of Regents and of the College committees at a date in April to be set by the President in consultation with the Secretary-General and the Executive Secretary. Dr. Irons announced that the American Board of Internal Medicine would meet at the same time. (The date has since been set for April 3-4, 1943.)

On motion by Dr. Fitz, seconded and regularly carried, it was resolved that the Board of Regents authorize the President to appoint a special committee, consisting of himself and the President-Elect, with the responsibility of taking the necessary steps to organize a committee on postgraduate instruction for doctors in the Armed Forces, as outlined in the resolution submitted earlier in the meeting by Dr. Bortz and adopted by the Regents.

President Paullin reported that on December 14 there would be a meeting of the War Participation Committee of the American Medical Association in Washington, at which he would present the above resolution. Thereafter he would contact the American College of Surgeons to obtain action from its executive committee. He expressed the hope that the program would be placed in action soon after the beginning of 1943, and he further gave the opinion that this is one of the most vital things that the College can do. He asked for authority to request these other organizations, if they are interested in this program, to donate funds to carry it through. On motion by Dr. Breed, seconded and regularly carried, Dr. Paullin and Dr. Irons were authorized to proceed accordingly.

ADJOURNMENT

Attest: E. R. LOVELAND, *Secretary*

ANNALS OF INTERNAL MEDICINE

VOLUME 18

APRIL, 1943

NUMBER 4

EDITORIAL INTRODUCTION

THE ANNALS OF INTERNAL MEDICINE in this number is participating in the publication of a symposium of articles on topics which are of interest jointly to both the medical and the legal professions.

Physicians in the practice of their profession repeatedly come into contact with the law. Too many of us have been quite unconscious or oblivious of these contacts. In most cases this appears to be of little immediate significance, as these contacts so rarely become actual conflicts. It is none the less important, however, that we should be better informed as to our duties and responsibilities under the law. It is hoped that this symposium will contribute to that end.

Special stress is laid on the importance of establishing "scientific proof," and on the care necessary to accomplish this in certain specific cases. By this is meant the assembling of precise dependable knowledge of the significant facts in any case under investigation. This is manifestly essential, and indeed is our first aim, for the proper treatment of any patient. This need becomes doubly evident, however, if the patient is the victim of some compensable injury, such as may result from exposure to some occupational hazard or accidental trauma.

The legal requirements and restrictions as to admissibility of evidence are designed primarily to insure that as far as possible this comes up to the standard of "scientific proof," that it is accurate, adequate and pertinent. The occasional failure to do this to the best advantage, particularly if medical problems are involved, neglect to utilize the newer discoveries of medical and other sciences, are most often due to mutual indifference or ignorance on the part of each profession of the problems and specialized knowledge of the other. As is pointed out more competently in the Preface and Foreword which follow, one major purpose of the symposium is to arouse the interest of the members of both professions in these and other common problems and to stimulate a coöperative effort toward their solution.

The ANNALS OF INTERNAL MEDICINE has been fortunate in having the services of Dr. Hubert Winston Smith as special editor of this symposium.

He has secured the coöperation of eminent writers from both professions, who have contributed authoritative articles in their special fields. Other articles in this symposium are being published simultaneously in Clinics and in Annals of Surgery. They are also being published in various legal journals. A master index of the entire symposium may be found elsewhere in this number. A few articles completed too late for inclusion in this number, it is expected will appear in subsequent issues of this journal.

PREFACE

If you are a strict individualist, you will think of law as a giant roof, pretty far above the ground, and mainly useful to shelter us from storms. You will be glad to see it kept high above our heads, even at the expense of having a little rain blow in occasionally. I think all Anglo-Saxons have something of this feeling. We do not care to surrender individuality or idiosyncrasy to gain a saltless Utopia.

But whatever may be the occasional conflict between individual freedom of expression and the social good, there need not be the serious contradiction that some would have us believe. Personal expression, on the whole, is very personal. Society can well afford to hold secure to John Doe his isolated retreat whereon hangs the sign: "Private property, trespassers keep out." This does not become incongruous by the fact that society has a motorcycle patrol on the transcontinental highway which runs by his door. There are spheres of individual life and spheres of social life. We may hope to add vitality and meaning to both at the same time.

Now in times past we have gone far by relying primarily on the analytical technic. Today we stand at the threshold of social synthesis. We who have rested content on the couches of our fathers must now bestir ourselves.

What more spirited or auspicious beginning could we make than to call the men of law and science to join their talents? It has seemed to me that we who belong to these two pursuits have a natural symbol, attractive to us both: *Scientific Proof*. This term has two applications: evidentiary and jurisprudential. Scientific Proof in the first sense implies making use of the best evidence available to determine basic questions of fact. It includes non-expert as well as technical evidence. In the second usage, Scientific Proof suggests the need for verifying facts by the most trustworthy methods before declaring doctrines of law involving "public policy," before writing or enacting a statute, or before promulgating a social theory. Scientific Proof is a high concept; if its requisites are flouted, science loses its chief bulwark and law its guarantee of justice. Roscoe Pound saw long ago, in developing his philosophy of Sociological Jurisprudence, that law is more than a passive thing. He saw that it can renew and revive itself, and that it can become an active force functioning to achieve "social control through law." We who would bring the legal and scientific traditions into close interaction are but giving content in one direction to his projected vision.

History shows us that neither tradition has ever escaped the impact of the other; now, however, we must replace accidental collision with specific coöperation. This purpose has motivated organization of the present Symposium Series on "Scientific Proof and Relations of Law and Medicine." We have tried to avoid vague and vaporous protestations of brotherhood. We have felt it more important that we confine ourselves to lively law-science

problems than to exchange felicitations. It is a work for all hands, and not for ours alone. We have used technical terms economically and clung to first principles to see if we could achieve a basic presentation intelligible to both professions and to the interested layman.

I must here thank each of my learned authors and each of the coöperating journals for adding luster to the effort.

HUBERT WINSTON SMITH,
Cambridge, Mass.

FOREWORD

Civilization is a cumulative activity. The mastery over nature which has enabled man to inherit the earth is an accumulation of experience and discovery set in order and developed by reason. As the accumulation goes on, it calls for increasingly minute division of labor both in investigation and discovery, and in systematizing and developing what has been discovered. The result is an extreme specialization of learning. It is no longer possible for any one to take all knowledge for his province even in his own field. He can only master his corner of it. Each minutely specialized discipline goes its own independent way without reference to any other.

Today there is an increasing tendency to break down the barriers which had come to separate the fields of learning. But this cannot mean that those working in any one may themselves know all that is required to be known or the accumulation in others in order to make their own more effective. It requires coöperation of the specialists in all fields in order to bring all knowledge into relation.

Legal precepts presuppose as given the facts to which they are applicable. When the facts are established a rule of law fixes the legal result. But the facts in any concrete controversy are seldom so given to us as to permit a mere mechanical process of applying the appointed legal precepts. They must be ascertained, and in ascertaining them courts have always had to call upon the medical profession for assistance in interpreting the evidence. To take a memorable example, in the English witchcraft trials of 1644 an experiment conducted by some skeptical persons threw doubt upon the testimony for the prosecution. Thereupon the court called Sir Thomas Browne, a leading physician of the time, and as the report tells us, "a person of great knowledge." After hearing the evidence and seeing the children claiming to be bewitched, he gave it as his opinion that they were, told of some recent cases in Denmark where there were the same manifestations, and explained how the witches had operated. The court could do no more than accept the opinion of so great an authority. But the lesson of judicial fallibility resulting from fallibility of the means of ascertaining the facts is always with us.

The Anglo-Saxon has been charged with muddling through even such practical matters as war. He is wont to leave as much as possible to experience instead of providing for things in advance. But the conditions of today call for planned and ordered coöperation of the lawyer and the man of science in doing systematically for types of questions what has been done unsystematically and often blunderingly for each case as it arose. If not, as Daniel Webster thought, the chiefest, justice is a chief interest of mankind. Coöperation toward making the administration of justice the best that it can be made is a duty of all of us.

ROSCOE POUND,
Cambridge, Mass.

SCIENTIFIC PROOF AND RELATIONS OF LAW AND MEDICINE*

By HUBERT W. SMITH, *Cambridge, Massachusetts*

THE anvil of the law has always resounded to the striking iron of science. Some tough metal has been beaten out there, sometimes into curious shapes, and few members of the populace can have failed to hear the reverberating blows or to see the cascading sparks which fly from those impacts. Despite all this, there is a cloud of uncertainty, an obscuration of terms, a lack of sharp definition which tend to invest vital aspects of law-science correlations with a curious mystery.

One of the fair sex who had attained to the pinnacle of 15th Vice-President of the American International Medico-Legal Congress, held in Chicago in 1893, showed that even she was more fervent about the cause than fully orientated. In response to an invitation from the chair, she delivered herself as follows:¹

Mr. President, Ladies, and Gentlemen: I know absolutely nothing about medical jurisprudence. Speaking, however, on general grounds, I know of no branch of science in which woman is more deeply interested. If any one has suffered from lack of such knowledge it is woman. The verdicts which are rendered against woman in the courts could, many of them, be traced to her ignorance of medical jurisprudence, and certainly we should welcome every research of that kind. I have been very much interested lately in the reports that have been published along this line of investigation. Many of them, I believe, will modify greatly the law in respect to its judgments on women. I believe woman should be tried by at least one of her peers, and I shall be very glad to welcome a law that medical women should sit on the bench in cases where judgment is to be rendered upon woman. I am stating this opinion in all humility, because I am utterly inadequate to speak on the subject of medical jurisprudence, but, you know, women 'rush in where angels fear to tread.'

If I had the wit and the courage of Bernard Shaw, I should try to match his tome entitled "An Intelligent Woman's Guide to Socialism" by a companion volume delineating the fruitful relations of law and medical science.

Even Justice Benjamin N. Cardozo, that rare judicial mind who added luster to the New York Court of Appeals and then to the United States Supreme Court by the quality of his legal opinions, kept at a cautious height when he spoke on "What Medicine Can Do For Law."² In considering what might come from the impacts of the two traditions, the Justice said: "Vain is the attempt to forecast here and now the lines of the transfigured structure."

* Received for publication February 13, 1943.

¹ Transactions of the American International Medico-Legal Congress of 1893 (1893) 11 Medico-Legal Journal 162.

² Address before New York Academy of Medicine, Bull. New York Acad. Med., 1929, v. 581.

I take up the task of describing this blacksmith shop, and the manner of things we might make there, with a certain zest. I think now we can reduce imaginings to reality. I have called to my aid luminous men of the law, masters of medicine, and stout fellows of science. Each has undertaken to illuminate some corner of the law-science workshop.³

To those who have contact with the judicial process, medical science is symbolic of the whole law-science diathesis. Inept words tend to obscure the breadth of law-medicine relationships. "Medical jurisprudence" is one such term. It has been used to describe a variety of things: sometimes the application of legal doctrine to medical practice, sometimes the special applications of medical knowledge to evidentiary problems which come before tribunals of the law. The term "Forensic Medicine" has a nice ring, and it is used abroad to signify the specialized applications of medical science in all varieties of legal proceedings. The American synonym, "Legal Medicine," makes the label sharper but raises an unwarranted inference that ordinary medicine may not be so legitimate. None of these terms conveys the true spirit or full content of law-medicine relationships, which in their totality represent social synthesis and correlation of a major variety. There is no universal authority on "Legal Medicine." In law-medicine, as in law-science relationships, we look upon a giant mosaic built up by many hands.

One of the cardinal activities of life is the making of proof. As in everyday life, the discovery of ultimate facts to guide action or decisions has a primary importance to the just working of the judicial process. All rules of substantive law assume the existence of basic facts on which to operate. Let these facts be distorted in their ascertainment, and the result may be as harsh as if defective legal principles were applied to agreed facts. For that reason, one signal aid which science may extend to law lies in the range of what we may call Scientific Proof. By Scientific Proof I mean the use of those scientific means and methods calculated to enable the accurate ascertainment of ultimate facts, either as a basis for settling private litigation (evidentiary), or as a means of forming or orientating legal or social policy (jurisprudential). Scientific Proof, so conceived, goes to the basis of action; it glorifies fact-finding functions and mechanisms; it gives solid substance upon which enlightened opinions may be formed, and it sets itself against all species of distortion in ascertaining and reporting facts. Its connected findings may well form a chain of criticism leading from fact to opinion, so tight and so strong that no speculative opinion can be inserted.⁴

³ The present paper introduces a Symposium Series on "Scientific Proof and Relations of Law and Medicine." As I proceed, I shall draw attention to studies prepared by fellow authors. An asterisk will be used immediately preceding each reference to a symposium article.

⁴ To borrow a homely phrase of the Texas rancher, our ideal in Scientific Proof is "to build the fence horse high, pig tight and bull strong." The primary ideal of Scientific Proof is to eliminate error and to secure truth by these means:

(1) The use of all appropriate methods of corroboration, with accent on diverse sources and types of evidence;

(2) The eventual grading of all types of evidence according to relative probative value;

In the evidentiary field, Scientific Proof will be found to revolve around three categories of problems, namely:

- I. Problems of identification (including existence and non-existence).
- II. Problems of causation.
- III. Problems of effects.

The specific content of each main series of problems differs according to the field of substantive law which gives rise to the litigation. This is a basic concept of all proof-making in courts of law. One must be able to state the ultimate facts necessary to prove a *prima facie* cause of action or defense. This has to do with burden of proof. The proponent of the issue must produce such quantum of evidence as will require the trial court to say mentally: "The evidence here is such that I cannot instruct a verdict for the antagonist. Remembering that as judge, I administer the law, but leave it to the jury to find the facts whenever there is substantial and conflicting evidence, I must charge the jury as to its legal function and leave it to those twelve men to retire, deliberate and find the true facts upon which to found their verdict." Substantive law doctrines thus operate to specify the essential facts to be proved, and so to determine the relevancy of particular evidence. Despite considerable overlapping in type problems and in methods, Scientific Proof breaks down into four fairly discrete categories. These are:

- I. Clinical Forensic Medicine
- II. Forensic Pathology
- III. Scientific Crime Detection
- IV. Modes and Mechanisms of Scientific Proof

I. CLINICAL FORENSIC MEDICINE AND SOME OF ITS OUTSTANDING PROBLEMS

Clinical Forensic Medicine embraces all varieties of medical practice which may yield evidence relevant to litigated issues by use of those tests and methods currently employed in diagnosing and treating patients. The expert witness is a practicing physician or surgeon, or a follower of one of the several specialties. He usually gains his evidentiary information from having examined or treated the party litigant for a non-fatal injury or disease.⁵ The lawsuit arises as a Workmen's Compensation claim, as a Tort

(3) Development of usable criteria and safeguards in respect to each type of evidence;
 (4) Promotion of complete understanding among courts, lawyers and experts of the pitfalls and potential errors of each species of evidence in order to enable wise cross-examination;

(5) Development of appropriate legal mechanisms and modes of trial;

(6) Repression of preconceptions and psychological predilections in the trial process and accentuation of the logical and scientific aspects of evidence. See Smith, H. W., *Components of Proof in Legal Proceedings*, (Feb. 1942) 51 Yale L. J. 537.

⁵ On occasion he may derive his opinion from examinations first made in the course of preparing himself to testify in court. Still again, under our practice, if he is properly qualified, he may express an expert opinion on the basis of hypothetical questions put to him by counsel, even though he has no personal knowledge of the case.

action for personal injuries, as a proceeding under a Life, Health or Accident Insurance policy, or in connection with some problem of status. Occasionally the suit is a wrongful death action, but in practically all cases the objective of the moving party is to recover compensation for alleged injury.

As long ago as 1909, 60 per cent of the cases tried in Superior Court in Suffolk County, Massachusetts, involved expert testimony. I dare say the percentage tends constantly to rise. Personal injury litigation accounts for a large fraction of these cases, but not for all of them. Practicing physicians have long been going to court as witnesses in actions brought to set aside wills or deeds for alleged mental incapacity at the time of execution, or to testify in criminal proceedings on the subject of the defendant's mental responsibility, or perhaps to give some influential finding or opinion based upon expert study of evidentiary problems.

1. *The Problem of Expert Testimony.* These impacts of law and science have given rise to thunderous reports emanating from the blacksmith shop and showers of sparks capable of burning the unwary. It is explained on the one hand that the sledge hammer of science is being used to hit glancing blows, or that it is an inadequate tack hammer not sufficient to beat out the metal. It is said by others that the anvil of law is slippery, or too narrow, or not made right to accommodate the materials upon which science must work.

The truth here does not lie within range of any single naïve explanation. Part of the difficulty arises from stupid or antiquated rules of evidence. In many states, as a result of ill conceived "privileged communication" statutes, an unscrupulous patient can obstruct justice by closing the mouth of his doctor on the witness stand.⁶ In most states, the hearsay rule has been carried too far. In others the cause of Scientific Proof has been obstructed by holding that taking involuntary body fluid or blood specimens violates the constitutional guarantee against self-incrimination or against unlawful search and seizure.⁷ These major vices in technical rules of evidence will soon go down before the frontal attacks of progressive legal scholars.⁸

Part of the difficulty in utilizing expert testimony springs from inadequate legal mechanisms. The lay jury is not qualified to determine scientific issues and much of the continuing friction springs from this maladjustment of the trier of fact to the questions he decides. Rather than play upon each independent defect, I prefer to consider the current position of expert testimony in its broader aspects and with particular reference to mechanisms of trial.

⁶ *Chafec, *Privileged Communications: Is Justice Served or Obstructed by Closing the Doctor's Mouth on the Witness Stand?* ANN. INT. MED., 1943, xviii, 606, 53 Yale L. J. (April 1943) —.

⁷ *Ladd and Gibson, *Legal-Medical Aspects of Blood Tests to Determine Intoxication*, ANN. INT. MED., 1943, xviii, 564, 29 Va. L. Rev. (April 1943) —.

⁸ *Morgan, *Suggested Remedy for Obstructions to Expert Testimony by Rules of Evidence*, 2 Clinics (April 1943) 1627, 20 U. of Chi. L. Rev. (April '43) —. See, also, Chafec, *supra*, note 6, and Ladd and Gibson, *supra*, note 7.

One must consider the nature of the ailment before he can specify the remedy. At the present moment, the doctor who goes to court as a witness is made a participant in a fast-moving adversary proceeding where a premium is put on quick thinking and categorical responses, and the devil usually gets the hindmost. If he shows a respectable doubt, his testimony is "conjectural"; if he is naïve, he may be trapped; if he has not the precious power of simplification, and the benefit of jury neutrality or sympathy, he may be misunderstood or misbelieved. If he is an expert on internal medicine, he may have to stand collateral cross-examination on the configurations of the tibia or some other bone which has no relation to his proper testimony. He may have to conform what should be a conditional answer to a "yes" or "no" because of the pernicious hypothetical question system.⁹ The medical man is primarily interested in treating and healing and is accustomed to having his opinions received with deference and respect. If, as it is said, 5 per cent of doctors now do most of the testifying in court, it is no matter for surprise.

Free selection of medical experts by parties litigant has tended to encourage "shopping around" for favorable experts, and this partisan bias is often more subtle than outspoken. Courts have plodded along, quite willing to recognize any holder of an M.D. degree as a universal expert on science. This naïveté is surprising, for the same judge who rules a general practitioner competent on his qualifying or voir dire examination, will take the train for Mayo Clinic if he stands in personal need of specialized surgery.

The truth is that Legal or Forensic Medicine calls for a type of knowledge and opinion that is often peripheral and new to the doctor's way of thinking. He has observed conditions and studied medicine principally in terms of therapeutics. He may have no justifiable opinion as to whether injury can produce a certain disease or as to the terminal effects in point of disability. If he has gone to court to accommodate an old patient, and is qualified on voir dire examination as a thoroughgoing expert, he may find it hard to confess the limits of his knowledge.

Suggested Remedies. How can these chasms be closed?

(1) The Need for Expert Referees.

The relation of injury to disease (proximate causation), and the assessment of terminal disability (fixing damages), pose scientific problems which should be settled by expert referees, medical specialists drawn from select panels. No lawyer need fear his immolation with advent of this change, for he would still participate in the informal hearings of the referees and have opportunity for his witnesses to be heard. The adversary system would be preserved, but with heavier accent on discovery of the true facts. Litigants could be hospitalized by the referee, examined by him or any of his nominees

⁹ In the Tuckerman will contest, tried before Judge McKim in Suffolk Probate Court (Mass.), attorney Robert M. Morse put to Dr. Jelley, a psychiatrist, what is reputed to be the longest hypothetical question on record. It concerned the mental condition of the testator, contained twenty thousand words and required three hours to propound. The witness answered: "I don't know." (April 1907) 5 Ohio L. Rep. 45.

and studied with scientific precision. The referee could be twins: a doctor and a lawyer acting together to see that evidence was fully developed while protecting fair hearing to the parties and the substance of major rules of evidence. All observations and findings would be reported in a "record," with conclusions listed in a separate section so as to permit review of the medical evidence. This review should be made by an appropriate medical expert serving as adviser to the trial judge when the latter has the medical record presented to him for "confirmation." Once confirmed, the medical findings should be final and not subject to disturbance by an appeal court. Confirmations could be resisted or set aside on grounds of fraud, accident, or mistake, but here the trial judge would lean on his medical adviser. It is eminently desirable to curtail review of medical findings to the trial court where proper access can be had to the litigant for reexamination.¹⁰

This device seems to be the ultimate goal of American jurisprudence. It would soon break the hold of mere advocacy and of shabby or ill-informed testimony. It would leave doctors to judge the testimony of doctors, eliminate futile efforts of the expert to descend to the lay juror's comprehension, and whet the interest of all socially minded doctors in the judicial process. The chief barriers to its realization are constitutional guarantees of jury trial.¹¹ The prospect of speedy reform is diminished by possible resistance of plaintiff's lawyers, but this fear should give way once the trial lawyer realizes that substantial verdicts will still be obtainable for genuine injury, but that claims based on fraud and malingering will be sifted out.

(2) Transitional or Mid-Way Reforms Not Involving Constitutional Amendment.

A. Impartial experts appointed by court.

A transitional reform is some variety of statute which authorizes a trial judge to appoint an impartial and qualified man or commission to investigate the physical condition or mental status of a party litigant. Such appointee acts as an officer of the court, and not as a privately employed expert. The device helps escape partisan pressure, gives the trial judge a chance to bring in authoritative consultants, and in several directions protects the purity of proof. It has the defect of keeping lay jurors as final arbiters of scientific

¹⁰ This device would permit a much closer surveillance of the excessiveness or inadequacy of monetary awards. The present appellate practice of determining whether the judicial conscience is "shocked," by looking to see what other courts have upheld in supposedly similar cases at other times and places involves several undesirable factors. It is not possible to make "book comparison" of any but the simplest injuries.

¹¹ Due process clauses, properly construed, require only a fair and regular mode of procedure and trial, and this need not be by jury. Abolition of grand jury indictment in criminal cases does not violate the due process clause of the Federal Constitution (Art. XIV: "Nor shall any State deprive any person of life, liberty or property without due process of law"), if the substitute procedure of prosecution on information is designed to give the accused a fair hearing. *Hurtado v. People of California*, 110 U.S. 516 (1884).

As to whether jury trial can be validly dispensed with in the trial proper of a criminal case, however serious the offense, see McGovney, *Cases on Constitutional Law*, (2d ed.) (1935), n. on p. 568.

Most state constitutions have specific provisions which operate to preserve the right to trial by jury in cases in which it existed at common law.

issues. It is shocking for the layman to hear that in many of our states as in Texas,¹² a trial court cannot appoint an impartial expert in a personal injury case to examine an unwilling plaintiff. Such a claimant can carry his case through court, to what may be a large verdict, with the defendant unable to secure independent confirmation of the reality and extent of injury. Fortunately the majority view is contrary, whether reached by common law, by statute, or under reformed rules of civil procedure such as those promulgated by the United States Supreme Court under a Congressional enabling act of 1934, for governance of the Federal District Courts.¹³

Massachusetts, one of the first states to provide for pre-trial examination of psychiatric cases by impartial experts,¹⁴ has found this method goes far to cure old evils.¹⁵

B. Certification of expert witnesses by medical profession as aid to "voir dire" examination.

The medical profession itself can add some straws to this broom. One who proposes to use a witness as an expert must establish his qualifications by preliminary questions. Opposing counsel may cross-examine the alleged expert to test his claims to special knowledge. At the conclusion of this voir dire examination, the trial judge must say whether the witness is a properly qualified expert, and his ruling will not be set aside except for substantial abuse of discretion. The medical profession itself could issue certificates of competency to its several members in respect to testimonial qualifications. If a general practitioner appeared in court as an authority on neurosurgery, a little probing would soon show that his own profession did not regard him as a proper expert witness on that subject. The intelligent trial judge, on conclusion of the voir dire examination, could rule the proffered witness incompetent with little fear of reversal by an appeal court.¹⁶ Even if the witness were allowed to testify, the lack of a certificate would be a proper subject for comment in arguing upon the weight which the jury should accord his testimony. No statute would be necessary to enable this salutary innovation, although legislation would be preferable empowering state licensing boards to issue such certificates after due hearing. In no case should the doctor who personally examined or treated a patient be debarred

¹² *Austin & N.W.R.R. v. Cluck*, 97 Tex. 172, 77 S.W. 403 (1903). This is not because a defendant has no right to the evidence, says the court, but because no legal sanction exists for compelling plaintiff to submit; silence of English common law is inferentially against such a jurisdiction, Texas statutes or constitution do not confer it, and a trial court cannot acquire it by implication from necessity. The spirit of the constitutional guarantee against unreasonable search would be violated.

¹³ U. S. Code Ann., Title 28, section 723c: Federal Rules of Civil Procedure for the District Courts of the United States. Preparation authorized: Act of June 19, 1934, c. 651, 48 Stat. 1064; put into effect Sept. 16, 1938.

¹⁴ Acts and Resolves of Massachusetts, 1921, ch. 415; Ann. Laws of Mass. (1942), C. 123, section 100 A. (The so-called "Briggs" law.)

¹⁵ Overholser, *The Briggs Law of Massachusetts: A Review and an Appraisal*, (1934-35) 25 J. Crim. L. & Crimin. 859-883.

¹⁶ Even if initially he has ruled the witness competent, the trial judge may reverse his ruling in the course of trial and intercept further questions when the trend of testimony shows the alleged expert to be incompetent. *Carboneau v. Lachance*, 307 Mass. 153, 29 N.E. (2d) 696 (1940).

from testifying. The prime purposes of the certificate method would be to grade competency and to exclude unqualified persons from giving opinion evidence as to the meaning of facts said to have been discovered by others.

C. Surveillance of expert testimony by professional "auditing" committee.

At the moment some medical witnesses are venturing opinions in court which they would not assert before medical societies. This double standard, when it exists, deprives courts of the scientific light they should have. When a doctor testifies that the moon is made of green cheese, as occasionally happens, he is either dishonest or ignorant, and needs to be disciplined by his professional brethren. In the past there has been no proper surveillance. Civil trials are attended by little or no publicity, and the improper medical witness has not had to face the just light of competent criticism.

Let it be said that all people competent to speak recognize that medicine is not an exact science, in its totality, but a mixture of science and art. There is much room for honest difference of opinion and for varying clinical judgments on open subjects. No one would hold all witnesses to subscribe to a single view in cases where good men may differ. But at last we come to outer limits of these justifiable differences, and no man is entitled to palm off as certainty what medical science itself knows to be purely conjectural and as yet without adequate proof, experimental or clinical. The test of improper testimony should be this: would medical men competent to speak on the subject in question consider the evidence given by Dr. X an acceptable view, scientifically, or would they consider it a prostitution of professional standards?

Each State Medical Society could appoint an auditing committee, including one member of the bar, to sample transcripts of medical testimony at periodic intervals in the medico-legal cases which reach the appeal courts. Witnesses found to have departed from professional standards would be subject to disciplinary action for cause, after due hearing, or to revocation or curtailment of their certificates as competent expert witnesses.

The mere presence of this real censorship mechanism would be as valuable as its actual use. It should be pointed out that surveillance of appeal records involves no improper probing or breach of confidence, for such documents are *public* records open to the freest inspection by any interested person.

D. Reformulation of medical science in terms of legal utility.

"Scientific Proof" does not imply that final answers are available for all medical problems which arise in court. All that we can expect to have is the benefit of the best evidence that the science of the given time can supply.

In times past the scientific accessions of medicine have been built largely on observations which have a therapeutic or curative implication. Even the great insurance companies cannot tell one how much the life expectancy of a person is shortened by the development of traumatic epilepsy following head injury. We have a great deal to learn yet about the general effect of

compromise settlements in curing or relieving traumatic neuroses.¹⁷ By sympathetic team work, we must study large groups of patients from new points of view to acquire much information of legal value that we cannot now extract from medical books.

In this Symposium Series, medical men of undisputed authority have endeavored to lay down basic criteria in respect to many of these problems, in a manner acceptable to both professions.¹⁸ In the future we shall be able to widen and lengthen this initial path with the great advantage to law and lawyers, and to expert witnesses.

2. *Problems of Mental Responsibility: Rules in McNaghten's Case.* In 1843, the House of Lords of the English Parliament called upon the learned judges to deliver an advisory opinion laying down proper tests for determining mental responsibility whenever a defendant prosecuted for homicide should raise the plea of insanity. The Lords addressed specific questions to the Judges. In the previous year McNaghten had been tried for killing Edward Drummond, whom he shot in the back, mistakenly believing he was firing upon Sir Robert Peel. Drummond was Peel's private secretary, and McNaghten was led to this violence by clearly substantiated delusions of

¹⁷ *Solomon, H. C., and Smith, H. W., Traumatic Neuroses in Court, 99 Am. J. Psychiat. (May-June 1943), —, 29 Va. L. Rev. (April 1943) —.

¹⁸ *Brahdy and Kahn, Clinical Approach to Alleged Traumatic Disease, ANN. INT. MED., 1943, xviii, 491, 23 B. U. L. Rev. (April 1943) —.

*Moritz, The Mechanisms of Head Injury, Ann. Surg., 1943, cxvii, —, 23 B. U. L. Rev. (April 1943) —.

*Denny-Brown, Factors of Importance in Head Injury, A General Survey, Clinics, 1943, ii, 1405, 29 Va. L. Rev. (April 1943) —.

*Munro, The Late Effects of Craniocerebral Injuries, A Consideration of the Criteria Necessary to Evaluate the Possible Causes, Ann. Surg., 1943, cxvii, —, 23 B. U. L. Rev. (April 1943) —.

*Ebaugh and Brosin, Traumatic Psychoses, ANN. INT. MED., 1943, xviii, 666.

*Solomon and Smith, *supra*, note 17.

*Marble, The Physician and the Workmen's Compensation Law, Clifford (1943, ii, 1441. Not in a law journal.

*Schwartz, Problems of Proof in Claims for Recovery for Dermatitis, ANN. INT. MED., 1943, xviii, 500, 41 Mich. L. Rev. (April 1943) —.

*Aldrich, Forensic Aspects of Burns with Special Reference to Approach of Terminal Disability, 29 Va. L. Rev. (April 1943) —.

*Ober, Some Practical Criteria for Use in Forensic Orthopedic Cases, Clinics, 1943, ii, 1476, 15 Rocky Mt. L. Rev. (April '43) —.

*Homans, Circulatory Deficiency in the Extremities in Relation to Medico-Legal Problems, ANN. INT. MED., 1943, xviii, 518, 21 N. C. L. Rev. (April 1943) —.

*Pollock, Examination of Motor and Sensory Function as Related to Opinion Evidence, Clinics, 1943, ii, 1424, 53 Yale L. J. (April 1943) —.

*Wolff, The Pain Threshold in Man, 99 Am. J. Psychiat. (March-April 1943) —.

*Joslin, The Relation of Trauma to Diabetes, Ann. Surg., 1943, cxvii, —, 15 Rocky Mt. L. Rev. (April 1943) —.

*Hertig and Sheldon, Minimum Criteria Required to Prove Prima Facie Case of Traumatic Abortion or Miscarriage, 117 Ann. Surg. (April 1943) —.

*Bennett, Medical Criteria Which Govern Relations of Trauma to Joint Disease, Clinics, 1943, ii, 1448.

*Warren, Minimal Criteria Required to Prove Causation of Traumatic or Occupational Neoplasms (Cancer), Ann. Surg., 1943, cxvii, —, 20 U. Chi. L. Rev. (April 1943) —.

*Merritt and Solomon, Relation of Trauma to Syphilis of the Nervous System, Ann. Surg., 1943, cxvii, —, 23 B. U. L. Rev. (April 1943) —.

*Cobb and Smith, Relation of Emotions to Injury and Disease, Medicine, (May 1943), —, —, — Harv. L. Rev. (Summer 1943).

persecution. He was tried before Chief Justice Tindal, filed a plea of lunacy, and was acquitted by the jury, which returned a verdict of "Not guilty, on the ground of insanity." The case provoked so much discussion in high quarters that the judges were called upon to declare, for guidance of courts in future cases, what a defendant must prove in a homicide prosecution to establish mental irresponsibility for his act. With frank temerity and open reluctance,¹⁹ the learned judges laid down certain principles regarding proof of mental irresponsibility sufficient to constitute a defense to a charge of murder (or other crime):

(1) "... The jurors ought to be told in all cases that: every man is to be presumed to be sane, and to possess a sufficient degree of reason to be responsible for his crimes, until the contrary be proved to their satisfaction";

(2) "... To establish a defense on the ground of insanity, it must be clearly proved that, at the time of the committing of the act, the party accused was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing: or, if he did know it, that he did not know he was doing what was wrong";

(3) As to "... persons who labour under such partial delusions only (i.e. in respect to one or more particular subjects or persons), and are not in other respects insane, we are of opinion that, notwithstanding the party accused did the act complained of with a view, under the influence of insane delusion, of redressing or revenging some supposed grievance or injury, or of producing some public benefit, he is nevertheless punishable according to the nature of the crime committed, if he knew at the time of committing such crime that he was acting contrary to law."²⁰

The rules laid down failed altogether to provide for certain contingencies:

(1) The justices did not recognize "irresistible impulse" or inability to refrain from the criminal action indulged, as any defense, so long as the actor still retained the ability to distinguish right from wrong.

¹⁹ The House of Lords had debated the subject of insanity as a defense to murder (March 6 and 18, 1843; see Hansard's Debates, vol. 67, pp. 288, 714); this led to a resolution to call upon the Judges for an advisory opinion, an extremely rare practice in English law, but not without precedent. The judges were required to frame their answers to specific questions, without benefit of argument by counsel, without hearing medical testimony and with but a short time for deliberation. Surely no more profound precedent was ever laid down in a law court on a flimsier foundation. It is to the credit of the judges that they were skeptical about their assignment. Mr. Justice Maule (one of the judges) said, 10 Clark & Fennelly, 203, at 204:

"I feel great difficulty in answering the questions put by your Lordships on this occasion:—First, because they do not appear to arise out of and are not put with reference to a particular case, or for a particular purpose, which might explain or limit the generality of their terms, so that full answers to them ought to be applicable to every possible state of facts, not inconsistent with those assumed in the questions: this difficulty is the greater, from the practical experience both of the bar and the Court being confined to questions arising out of the facts of particular cases:—Secondly, because I have heard no argument at your Lordships' bar or elsewhere, on the subject of these questions; the want of which I feel the more, the greater are the number and extent of questions which might be raised in argument:—and Thirdly, from a fear of which I cannot divest myself, that as these questions relate to matters of criminal law of great importance and frequent occurrence, the answers to them by the Judges may embarrass the administration of justice, when they are cited in criminal trials. . . . I shall proceed to give such answers as I can, after the very short time which I have had to consider the questions, and under the difficulties I have mentioned; fearing that my answers may be as little satisfactory to others as they are to myself."

²⁰ McNaghten's Case (House of Lords) 10 Clark and Fin. 200 (1843).

(2) The concept of attenuated responsibility was not recognized and the psychopathic personality was entirely ignored.²¹

English courts steadfastly continue to pay lip-service to McNaghten's rules. Most American courts have done likewise, except for those jurisdictions which have broadened the original categories to include the further exculpatory ground of irresistible impulse of one kind or another.

These rules, pronounced with misgivings, did a great deal to sabotage law-medicine relationships. A host of psychiatrists such as Emil Kraepelin (1856-1926) advanced the description of clinical entities in the field of psychiatric disorders. The rules in McNaghten's case remained static. They were assaulted by such psychiatrists as Maudsley and criticized by such criminal law writers as Stephens. They were studied by Select Reform Committees in England and impugned in America by Sheldon Glueck²² and other criminologists.

There is no doubt that several sharp arrows can be shot at this target. It is erroneous to assume that one can abstract single mental faculties in judging mental health. Delusions should be regarded as a general symptom of mental disorder and not be given limited evidentiary value. Inability to abstain from wrongful conduct runs to volition itself and is as basic as inability to form a moral judgment. The criminal law has always

²¹ The reader may suppose that the psychopathic personality had not then been recognized as a psychiatric entity, but medical men in England as early as 1829 had demarcated the condition from irresponsibility or insanity due to disease.

Sampson, in his *Criminal Jurisprudence in Relation to Mental Organization*, London (1841) at p. 7 had said:

"In the Richmond Lunatic Asylum, Dublin, Mr. GEORGE COMBE saw a patient, in 1829, who had been confined for ten years. He exhibited a total want of moral feeling and principle, yet possessed considerable intelligence, ingenuity, and plausibility. He had been a scourge to his family from childhood—had been turned out of the army as an incorrigible villain—had attempted the life of a soldier—had been repeatedly flogged—and had since attempted the life of his father. Respecting this man, Dr. CRAWFORD, Substitute Physician at the Asylum, made the following remarks. *'He never was different from what he now is; he has never evinced the slightest mental incoherence on any one point, nor any kind of hallucination. It is one of those cases where there is great difficulty in drawing the line between extreme moral depravity and insanity, and in deciding at what point an individual should cease to be considered as a responsible moral agent, and amenable to the laws. The governors and medical gentlemen of the Asylum have often had doubts whether they were justified in keeping him as a lunatic, thinking him a more fit subject for a bridewell. He appears, however, so totally callous with regard to every moral principle and feeling, so thoroughly unconscious of ever having done any thing wrong, so completely destitute of all sense of shame or remorse, when reproved for his vices or crimes, and has proved himself so utterly incorrigible throughout life, that it is almost certain that any jury before whom he might be brought, would satisfy their doubts by returning him insane, which in such a case is the most humane line to pursue. He was dismissed several times from the asylum, and sent there for the last time for attempting to poison his father; and it seems fit he should be kept there for life as a moral lunatic: but there has never been the least symptom of diseased action of the brain, which is the general concomitant of what is usually understood as insanity. This, I consider, might with propriety be made the foundation for a division of lunatics into two great classes,—those who were insane from original constitution, and never were otherwise; and those who have been insane at some period of life from diseased action of the brain, either permanent or intermittent.'*"

Benjamin Rush, father of American mental science, was one of the first to point out that disorders of the moral sentiments may be congenital and equivalent to partial imbecility, and he suggested that "moral imbecility" better described such cases than did the term "moral insanity." Rush, *Medical Inquiries and Observations Upon the Diseases of the Mind*, Phila. (1812).

²² Glueck, *Mental Disorders and the Criminal Law* (1925).

required a "mens rea," or bad state of mind, as an ingredient of felonies, and some voluntary act to which moral culpability can be attached. It was anomalous from the start that irresistible impulse should have been excluded from McNaghten's rules.

The more difficult exercise is not to assault these old and vulnerable redoubts, but to explain why and how they have been able to withstand capture for so long. It would be a grievous error to assume that men of law have been obstinate or obtuse. Sir Matthew Hale (1609-1676), Lord Chief Justice of the Court of King's Bench in England, wrote on lunacy long before McNaghten's rules were pronounced. He was keenly aware of the subtle gradations in mental responsibility. Indeed, he said:

"... It is very difficult to define the invisible line that divides perfect and partial insanity; but it must rest upon circumstances duly to be weighed, and considered both by the judge and jury, lest on the one side there be a kind of inhumanity toward the defects of human nature, or on the other side too great an indulgence given to great crimes."²³

The great English judges were almost all recruited from among the leading trial lawyers. They were men with a grasp of practical affairs, and doubtless many of them had dinner companions among the eminent medical men. We cannot believe that they had no inkling of the disparity between the legal and medical approach to mental disease. The truth is that McNaghten's rules are not philosophical concepts, but mere products of the mode of trial under our adversary system. Lay jurors have long had the responsibility of passing upon the weight and credibility of expert testimony.²⁴ This they do under a proper charge delivered by the trial court at

²³ Hale, *The History of the Pleas of the Crown* (1736).

²⁴ In Roman law we find evidence that scientific issues were referred to expert referees for decision. See Dig. 25.4.1 pr. where the case was as follows:

[Rutilius Severus declared that his wife, who had divorced him, was pregnant. This she denied. Rutilius wanted to claim the child when it was born. Apparently his wife did not want him to do so and for that reason denied that she was pregnant.]

"Rutilius Severus seems to desire a new thing in applying for a custodian for his wife, who divorced herself from him and alleges that she is not pregnant; and so nobody will wonder if we also suggest a new counsel and remedy. Therefore if he persists in the same demand it is most convenient to choose the house of a most respectable woman in which Domitia shall come, and there three midwives of proven skill and honesty, who will be selected by you, shall inspect her. And if indeed all or two shall report that she appears to be pregnant, then the woman shall be persuaded that she accept the custody as if she herself had demanded it. But if she does not give birth the husband may know that it pertains to his odium and reputation that not undeservedly he may seem to have attempted this as some kind of an insult to the woman. But if all or most report her not to be gravid (pregnant) there will be no cause for custody." Rescript of the Emperors Marcus Aurelius and Lucius Verus to Valerius Priscianus, urban prefect (161-169 A.D.).

In the time of Gordian (238-244 A.D.) we find this provision:

"To soldiers once dismissed for cause, readmission on the ground of recovery of better health is not customary since they are not carelessly dismissed but only those who are found to have acquired a defect according to the report of physicians and also on the diligent investigation of a competent judge." C. Just. 12.36.6.

It was further provided that in case doubts arose as to the authenticity of deeds, it should be necessary to compare the handwriting of the subscribers. Nov. 73.7 pr. (A.D. 538).

References to use of experts in the Roman legal texts can be found in Wetzell, *System des Ordentlichen Civilprocesses* (1878) 528, n. 11.

In Canon Law it has long been customary for the judge in matrimonial cases involving alleged impotency or non-consummation of the marriage, to establish the facts by ordering

the close of the case, shortly before they retire to the jury room to consider their verdict of "guilty" or "not guilty." Before a lay judge can frame an intelligible charge for the guidance of lay jurors, he must be able to carve out some rule-of-thumb classifications or categories which these jurors can apply to the evidence to be valued. Immediately we import a forced certainty of statement into a realm which is essentially uncertain and variable.

This practical problem of proof has much to do with the unwillingness of English courts to embrace the doctrine of irresistible impulse. There is no doubt that violent disappointments in love and other psychological pressures can drive a person to inhuman conduct as irresistibly as disease, as Louis Proal, the French judge, so brilliantly showed in his "Passion and Criminality."²⁵ But English courts have been afraid to get out on these uncharted seas, where all criteria are dim, and degrees of responsibility are not provable by objective evidence. They have not paid so much regard to the paralysis of volition as to the suspected tinge of culpability in allowing oneself to take the first step. Thus, one who voluntarily partakes of alcohol and kills in a drunken rage may, if he lacked the required malice aforethought or specific criminal intent, have his offense mitigated from first to second degree murder or to manslaughter, but in most jurisdictions he cannot set up his drunken state as a complete defense and thereby gain acquittal.²⁶ If his voluntary intoxication leads to the independent disease of delirium tremens, and as a result of an automatic state induced thereby, he kills another, he has a complete defense.²⁷ The culpable first step has merged

bodily inspection of one or both parties by court-appointed experts. See Gasparri, *Codex Juris Canonici* (1918 ed.).

Canon 1792: "The service of experts must be employed whenever the law or the judge demands their interrogation and opinion for the purpose of establishing some fact or determining the true nature of the thing."

[This canon apparently originated in the Decretals of Pope Gregory IX (1145-1241). The Decretals were drawn up between 1230-1234 A.D.]

The early common law provided a writ for a jury of matrons *de ventre inspiciendo* in proper matrimonial causes (Bracton, *De Leg. lib. ii fol. 69*).

Indeed, throughout the fourteenth century in London, courts used special juries of experts drawn from a particular trade to hear causes involving trade disputes. See, Riley, *Memorials of London and London Life in the 13th, 14th and 15th Centuries* (1868).

In 1345, an English court, in an appeal of mayhem, called London surgeons to help them determine whether a wound was fresh. Anonymous, *Lib. Ass.* 28 pl. 5 (28 Edw. III).

These facts are the more significant when we realize that the jurors originally heard no witnesses and were themselves free to go about investigating the facts both before and during trial. It was not until the middle of the 15th century that it became customary to summons witnesses. It was not until after 1600 that the direct and influential use of experts began to succumb to the present evidentiary restrictions, with the result that scientific proof became merely advisory to the lay jury, and reduced to the status of open competition with lay testimony. The foregoing English cases, and others, are mentioned in Hand, *Historical and Practical Considerations Regarding Expert Testimony*, (1901) 15 *Harv. L. Rev.* 40.

Any trend forward, anachronistically, must be a trend backward, to the more direct mechanisms which the law had prior to 1600.

²⁵ Proal, *Passion and Criminality*, published by Charles Carrington, 13 Faubourg, Montmartre, Paris.

²⁶ Singh, *History of the Defense of Drunkenness in English Criminal Law*, (1933) 49 *L. Qu. Rev.* 528. For American decisions see *E. V. R.*, *Intoxication in Mitigation of Homicide*, (Sept. 1941) 2 *Qu. J. Alcohol* 396.

²⁷ *Regina v. Davis* (Northeastern Circuit, Newcastle-upon-Tyne), 14 *Cox C. C.* 563 (1881). Trial before Justice Stephen, the same Sir James Stephen famous for his "History of the Criminal Law" (1883).

into a disease state which human agency cannot control, and furthermore there is a guarantee of authenticity when the aberrant mental state is a familiar symptom of a standard disease

One cannot fairly say that currently the English courts reject "irresistible impulse" in toto; possibly that defense has full vitality in England in all cases in which transient mania, or irresistible impulse, is the explosive symptom of an ascertainable, preexisting disease such as delirium tremens, epilepsy, or one of the psychoses³⁸ It is at the brink of mere psychologic motivation that the English courts draw back, and there is much to be said for their hesitancy if we orientate rules by practical considerations of sound proof-making

The conflict we have here between current law and good psychiatry does not arise from obtuseness of the legal mind, nor from any desire of law to poach upon medical preserves, but from understandable consequences of trial by jury Assume lay jurors are to continue trying scientific issues, and you will find a natural and understandable hesitancy about giving up the pat, albeit, illusory certainty of McNaghten's rules Arrange for lunacy problems to be delegated to psychiatrists acting as expert referees, and this delegation will draw after it a conceded right to erect new criteria suitable to guide the new trier of fact In the judicial process, definitions have but one function—to serve as sign posts for the trier of fact Those who would destroy McNaghten's rules should make a flank attack rather than a frontal assault, by seeking legislation designed to make the accredited psychiatrist an expert trier of fact in lunacy issues

When we turn to the law in action in England, we discover that McNaghten's rules do not work oppressively as against a particular defendant One would imagine that few prisoners could prove a defense of lunacy In practice the fact is otherwise, and it would appear that the jury uses its verdict of "guilty, but insane" in a generous manner, sometimes to save from capital punishment prisoners not believed to be free agents or grossly culpable in committing the crime Mr Justice Darling recognized that juries use this verdict as an escape device when he pointed out that in many criminal asylums there are defendants "as sane as the Judges who tried them"

"147 From a table issued by the Committee on Insanity and Crime, appointed in 1922, we find that, taking the figures for the 22 years 1901 to 1922, the number of persons on trial for England and Wales on murder charges was 1,445, of which 134 were found insane on arraignment and 351 were found guilty but insane, being a total percentage of 9 273 insane on arraignment, and 24 292 guilty but insane, or 33 663 per cent in all insane

³⁸ Frequently these cases involve such "automatism" as to deprive the actor of knowledge of "the nature and quality of his act," or the mental state is such that experts do not hesitate to say that the accused was unable "to distinguish right from wrong" Opinions of the higher English courts have not yet covered irresistible impulse, as a third category, in a satisfactory or definitive way Yet we cannot overlook the fact that in 1924 the House of Lords defeated Lord Darling's "Criminal Responsibility (Trials) Bill" intended to establish irresistible impulse due to mental disease as an additional legal defense.

"148 Coming to Scotland, we find that, in the 20 years, 1910 to 1929, 249 persons were indicted and brought to trial for murder, of whom 22 were found guilty of murder, 104 of culpable homicide, and 23 of other crimes, 41 were found insane in bar of trial, and 9 at time of act, while 49 were assolized Those declared insane were thus 20 per cent of those indicted " ²⁹

It would be an interesting experiment to subject these cases to independent psychiatric study, to determine how many of these acquitted persons actually are insane If only 10 per cent should be found to be so, the only significance would be that 23 per cent of this group have been committed to asylums rather than to the hangman, for in England, since 1800, an acquittal on the ground of insanity makes the defendant subject to consignment to an asylum "during His Majesty's pleasure " ³⁰

Assume that a defendant has been convicted by a jury due to literal application of McNaghten's rules Since the Criminal Appeal Act of 1907 ³¹ the English Court of Criminal Appeal has had power to hear new evidence in reviewing the conviction, ³² and the further power to substitute the jury's verdict ³³ The Court has exercised this jurisdiction sparingly, but it is a not uncommon thing for the Court in affirming the conviction within the framework of McNaghten's rules to invite intervention by the Home Secretary ³⁴ Under the Criminal Lunatics Act, 1884, ³⁵ the Secretary of State (Home Secretary) is empowered after conviction and before execution of sentence to intervene, appoint a committee of medical men to examine into the prisoner's present sanity, and to substitute commitment in an asylum in lieu of the court penalty In this investigation, the medical men apply psychiatric standards as they would in studying any other case recommended for commitment under a lunacy certificate We now have the somewhat farcical spectacle in England of courts paying continued lip service to McNaghten's rules because of respect for precedent and practical problems of proof raised by jury trial, while inviting an auxiliary administrative agency to step in and apply modern psychiatric tests after the court is done!

Unfortunately in many American states we have not been so adroit in developing escape mechanisms for McNaghten's rules, most often we have

²⁹ Report from the Select Committee on Capital Punishment, House of Commons (1929-30) 36 Printed by H M Stationery Office (1931)

³⁰ Before 1800 in England, an acquittal on the ground of insanity would enable the defendant to go free without any protection for society The "Criminal Lunatics Act" of 1800, in England, provided that a jury, in acquitting a defendant accused of felony, must make it clear whether their action were taken because they found the accused person was insane at the time he committed the act If so, the defendant was committed to an asylum and detained "during His Majesty's pleasure" The special form of verdict, "guilty, but insane" was specified by the "Trial of Lunatics Act" (1883) s 2

³¹ 7 Edw 7, c 23

³² Exercised in *Rev v Holt* (Crim App), 15 Cr App R 10 (1920)

³³ As in *Rev v William Hopper* (Crim App), 11 Cr App R 136 (1915) Defense accident, jury verdict murder, substituted verdict entered on appeal manslaughter, with sentence reduced to four years' penal servitude In *Rev v Beard* (Crim App), 14 Cr App R 110 (1919), D while intoxicated raped a girl and apparently strangled her to death by accident Jury verdict of murder, reduced on appeal to manslaughter because of error in trial court's charge

³⁴ As in *Rev v Lumb* (Crim App), 7 Cr App R 263 (1912), *Rev v Boss* (Crim App), 16 Cr App R 71 (1921)

³⁵ 47 & 48 Vict, c 64

preserved the facade without eroding away the substance. The time has come in both countries for recognizing psychiatric appraisal of court cases as a problem to be farmed out to expert referees.

I must not leave this subject without subscribing to the belief that the "trial-defense-acquittal" formula is fundamentally erroneous. Culpability or fault was a cardinal juridical concept of the past two centuries, but it is steadily shrinking in authority as a touchstone of legal thinking. In the field of criminology, "danger to society" is the more important consideration.³⁶ The defendant who shows attenuated responsibility, the weakling who gives way to "irresistible impulses" in response to ordinary social stimuli, the psychopathic personality, whose whole reaction to life is tragically warped, sometimes in the most cruel and sadistic ways—these persons cannot scientifically be *punished* as free agents, they cannot, as a rule, be salvaged for "open" society by reform, and they are better looked upon as special psychiatric cases too dangerous to remain at large. The test of culpability or fault in committing the crime has no real meaning in the presence of one of these permanent personality defects.³⁷ Our preoccupation must be with early discovery of these pre-delinquents and the making of more certain arrangements to segregate and control them.³⁸ To protect innocent members of society against their violent crimes calls as much for preventive methods as for mere permanent detention after the heinous crime is done.³⁹

3 Medical Criminology and Penology Physicians have had a conspicuous part in the ceaseless probing and questing for the basic causes of crime.⁴⁰ It would seem now that multiple factors are usually involved in the pathogenesis of a criminal career. Biological factors or actual disease may play an insignificant or an important rôle in a particular case.⁴¹

³⁶ In master-servant cases, Workmen's Compensation Laws have substituted "injury from accident arising in the course of employment" as the basis of liability in lieu of the employer's negligence.

In the field of Domestic Relations, many states now permit divorce where the two spouses live apart for a statutory period, without regard to any fault of either. Still other jurisdictions have provided by statute that continuing insanity of one spouse arising after the marriage ceremony is ground for divorce.

As insurance against the perils of life becomes a social function, fault as a risk-fixing device will be much eroded, if not destroyed. If, as and when that phase is reached, we may still expect as a matter of social policy, that one who wilfully injures himself will be debarred from recovering compensation.

³⁷ Capital punishment in such cases is inappropriate, but as the psychopathic personality is not technically insane under McNaghten's rules, executive clemency is necessary to change the death penalty to life imprisonment. Governor Ritchie of Maryland saved Herman W. Duker, a psychopathic murderer, from capital punishment by such last-minute intervention. Ulman, *A Judge Takes the Stand* (1936), Appendix, p. 273.

A more recent case, in Massachusetts, was that of Woodward, a psychopathic juvenile, who killed a young girl by slow torture, and escaped the supreme penalty, after conviction of murder only by last minute commutation of his sentence to life imprisonment.

³⁸ See Thom, *Irresponsibility of Juvenile Delinquents*, *Am. Jr. Psychiat.*, 1942, 49, 330.

³⁹ For prolonged studies along this line from which the authors derive a formula of "predictive factors" intended to guide juvenile courts, see Sheldon and Eleanor Glueck, *Juvenile Delinquents Grown Up* (1940). (Based on statistical studies of 10 year records of 1,000 cases.)

⁴⁰ See Fink, *Causes of Crime: Biological Theories in the United States, 1800-1915* (1938).

⁴¹ Dr. Francis Joseph Gall (1758-1828) has been described as the founder of criminal anthropology. His discoveries in the anatomy of the brain won the highest praise of both

Despite the deep interest of lawyers and doctors in these subjects, there has been no national law passed providing for uniform examinations, consistent classification of offenders, or centralized collection of statistics. Even in the detailed judicial statistics of England one cannot find such data. There is a need, too, for the medical penologist, for studies of prison populations should go beyond etiology of crime to the formation of enlightened decisions regarding proper segregation of prison inmates and their fitness for parole.⁴² At the moment, no one test or examination seems adequate to provide the desired personality blueprint, and improvement of methods is one of the central problems in this field.

In going through medical literature, one observes certain recurrent flaws in many studies dealing with relation of mental defect to crime.

(1) The investigator often fails to enumerate associated mental defects. A recent patient in Boston City Hospital, who had been in prison several times, was a chronic epileptic, suffered from delirium tremens from long indulgence in alcohol, and was a psychopathic personality. Each of these defects has an independent relation to criminal propensity, and it would be misleading to list the subject merely as an epileptic.

(2) In some cases a proper doubt may arise as to the adequacy of the test methods.

(3) Frequently the investigator does not correlate the particular defect or mental state with commission of the crime. To be considered significant in point of etiology, the defect should have been a substantial cause of the dereliction.⁴³

Bischoff and Cuvier, but it was his bad fortune to be remembered principally for his rapidly discredited theories of phrenology.

Cesare Lombroso had attained to a position of eminence by the end of the last century through his anthropological investigations of criminals. He described various anomalies in the brains of criminals, but he failed to control his studies, and did not realize that brains of normal, law-abiding citizens show similar anomalies. Virchow predicted that his work would one day fall into low esteem as compared with the broad general contributions of Gall. Dr C B Griffiths, Charles Goring, and other English prison medical officers systematically measured 3,000 subjects under direction of Professor Karl Pearson, using certain controls. In their published results in 1913 they said: "Our inevitable conclusion must be that there is no such thing as a physical criminal type." Interest in the anthropological approach more broadly conceived has been freshly stimulated by the careful researches of Dr Earnest A Hooton, Professor of Anthropology at Harvard.

Phillipe Pinel (1745-1826) attacked problems of criminality from the vantage point of an alienist, as did Esquirol (1722-1840) the French psychiatrist. The latter produced in 1838 his well-known treatise, "On Mental Diseases in Their Medical, Hygienic, and Legal Relations." Maudsley and Mercier in England continued to study the relation of crime to insanity, and in America we have had several hundred studies devoted to the relation of mental defect to criminality. Some investigators have studied the I Q's of prison populations, others have combined such psychometric methods with detailed medical examination and psychiatric diagnosis.

⁴² For an excellent study of this type, see Branham, *The Classification and Treatment of the Defective Delinquent*, (1926) 17 J Crim L & Crim 183. For an important earlier study, see Glueck, Bernard. *A Study of 608 Admissions to Sing Sing Prison*, (1918) 2 Mental Hygiene 85. Rockefeller Foundation has carried out important surveys of prisoners in various institutions of the several states.

⁴³ A model study in this regard is the critical analysis by Dr W Norwood East of the main and subsidiary causes of attempted suicide, based on his personal examination and investigation of one thousand consecutive cases admitted to Brixton prison, in England. Dr East found the major causes and motivations of attempted suicide to be as follows: 1. Alco-

It is safe to say that mental disease is very rarely a sole cause of criminality. As Dr A. Warren Stearns, the experienced forensic psychiatrist, puts it, mental aberrations may cause the subject to become involved in episodes which propel toward criminal behavior. Certain mental conditions seem to predispose the subject to violent reactions, whereas states due to senile deterioration are more often associated with disorderly conduct or vagrancy. This is illustrated by a table prepared some years ago by the New York State Hospital Commission, showing distribution of crimes among clinical diagnoses of 646 persons admitted to Matteawan Hospital, New York, an institution for the criminally insane.⁴⁴ The table follows:

PER CENT DISTRIBUTION OF CRIMES AMONG CLINICAL GROUPS

Crime	Per Cent of Total Crimes						
	Senile	General Paralysis	Alcoholic	Manic-depressive	Dementia Praecox	With Constitutional Psychopathic Inferiority	With Mental Deficiency
Homicide (all forms)	—	2.9	17.6	2.9	32.4	14.7	17.6
Assault (all forms)	—	3.8	24.1	7.6	25.3	17.7	6.3
Burglary	—	13.2	—	7.9	39.5	23.7	5.3
Larceny (all forms)	1.3	22.8	5.1	6.3	24.1	15.2	7.6
Public intoxication	2.9	2.9	70.6	—	5.9	5.9	—
Disorderly conduct	2.4	13.4	17.1	12.2	17.1	17.1	7.3
Vagrancy or prostitution	8.5	15.4	13.8	4.3	35.1	6.9	7.4
All crimes	3.6	11.5	16.9	7.3	25.5	14.7	7.4

That mental defect usually is only one of several multiple causes of crime is suggested by a rather neat comparison. Various studies show that mental defect has some relation to the etiology of major crimes of violence in a substantial percentage of cases.⁴⁵ Studies of the inmates of mental institutions, on the other hand, show a markedly lower incidence of such behavior.⁴⁶

holic impulse with amnesia (141), 2 Alcoholic impulse—memory retained (171), 3 Post-alcoholic depression (31), 4 Out of work (112), 5 Destitution (64), 6 Domestic trouble (120), 7 Ulterior purpose (61), 8 Fear of imprisonment or on arrest (41), 9 Business worries (27), 10 Depression from various causes (20), 11 Other causes (shame, mistake under alcohol) (7), 12 Weak-mindedness (46), 13 Neurasthenia (8), 14 Epilepsy (10), 15 Morbid mental states (18), 16 Insanity (123).

East, *Medical Aspects of Crime* (1936), Ch. V, p. 141.

⁴⁴ The table is reproduced from Nolan, *Some Characteristics of the Criminal Insane* (May 1920) 5 *The State Hospital Quarterly* 362. It covers 646 patients, a rather small series, and the table is reprinted to show efforts at correlation of mental defect with type of crime, not as proof of exact relationships.

⁴⁵ Dr. A. Warren Stearns, during his tenure as psychiatrist of Massachusetts State Prison, made an intensive study of 100 prisoners, 58 of whom had been convicted of manslaughter, 39 of second degree murder and 3 of first degree murder. He found that 20 per cent were drunk when the crime was committed, and that "twenty of the series showed well marked departure from normal mental condition, nine being definitely insane, three feeble-minded, eight presenting personality disorders of so gross a character as to limit their responsibility." Stearns, *Homicide in Massachusetts*, *Am. Jr. Psychiat.*, 1925, n. 725.

See also, *Stearns, *Medical and Social Factors in Crime*, *ANN. INT. MED.*, 1943, xviii, 599.

⁴⁶ Elwell found that very few homicides were committed in the asylums of Ohio, or of other states, and drew the conclusion that not one out of a thousand of those who commit murder are actually insane, but become conveniently afflicted with mental disorder for purposes of trial. Elwell, *Epilepsy as a Defense for Crime*, (1890) 8 *Medico-Legal J.* 55. It is

Part of this difference is due to repression, segregation, careful guarding by hospital personnel, but much of it seems fairly attributable to the fact that the inmate is now unable to become involved in those social transactions which give rise to the multiple stimuli that propel toward criminal behavior. *Protect the lower fraction of the social structure from the fierce pressure of a competitive system, alleviate the distorting and disturbing tensions which the less than average person feels, treat criminality by curing widespread maladjustments, and it is reasonable to believe that you will see a sharp fall in crime and in admissions to mental institutions.* Deterioration of the inadequate personality is partially a symptom of a social organization not fully adapted to protecting its weaker members.

On the horizons of medical criminology, we can see an approaching emphasis on functional studies. In 1929 Berger published his first paper describing the action currents or "brain waves" given off continuously by the cerebral tissue.⁴⁷ The electro-encephalogram is a graphic tracing of these waves which can be made by a competent laboratory technician, without risk of injury to the patient. This is done by properly applying electrodes to various locations on the patient's cranium, and taking off the action currents for automatic tracing onto a moving tape by a relatively simple recording device.

Dr William Lennox and Dr F A Gibbs and his wife, all of Boston, among other leading workers, have been amassing great numbers of normal and abnormal tracings for some years to the end of developing criteria of interpretation. Abnormal waves emanating from a particular region of the brain help localize a suspected brain tumor. The workers mentioned postulate that epilepsy, one of our most enigmatic diseases, must be considered to be a cerebral dysrhythmia with characteristic "brain wave" patterns. The implications for Scientific Proof, present and future, of this line of research should be clear.

For instance, we have long known medically that some persons afflicted with epilepsy may commit violent crimes during phases of the disease which momentarily destroy their mental responsibility. The epileptic may commit such a crime during a disoriented state of "epileptic furore" or frenzy, he may commit it during the post-seizure "clouded" state when his sensorium is radically deranged but he is nevertheless able to walk and perform actions as in a dream. Again, in lieu of his usual convulsion or lapse of consciousness, the epileptic may have a substituted attack called a "psychic equivalent," during which he is temporarily disoriented but may appear outwardly normal except for a glassy stare, a certain incoherence of speech and slightly incongruous conduct. While in the grip of one of these states, the epileptic

interesting to note that Dr Walter Channing, responding to the author's questionnaire, took sharp issue with this opinion and cited experience of the New York courts in support of his contrary belief that an appreciable percentage of homicides are committed by insane persons. Id at 61.

⁴⁷ Berger, H. Ueber das Elektroencephalogramm des Menschen, Arch f Psychiat, 1929, 100, 527.

is subject to so-called automatism, and may perform involved acts and fairly complex crimes without insight or power to abstain. We do not understand all the mental phenomena involved here, but we can say if the case is genuine that the unfortunate perpetrator of the homicide at the time of his conduct was both unable *to appreciate the nature and quality of his act* (the more basic test under McNaghten's rules) and *to distinguish right from wrong*.

In more than one celebrated murder prosecution both in England and in America the defense of epilepsy has been injected, which is formally raised under a plea of insanity⁴⁸. Two important problems of Scientific Proof arise

(1) Is the defendant a true epileptic or is the history of past "fits" fabricated, or if true, are the attacks described referable to some other disease capable of producing occasional convulsions?

(2) Assuming defendant is a true epileptic, was his epilepsy so operative at the time of the alleged criminal act as to destroy mental responsibility? Since there are thought to be 600,000 epileptics in the United States alone, it is easy to see that an epileptic may commit a deliberate murder during a lucid interval between seizures and try to escape criminal penalties by falling back on a false plea that the conduct occurred during a period of "automatism."

The first problem can usually be solved by application of the electroencephalogram. He might have no spontaneous seizures during his surveillance in prison. But in the laboratory he can be asked to hyperventilate (prolonged rapid breathing) or innocuous materials can be given without

⁴⁸ *English cases* *Rex v James Hadfield*, 27 Howell's State Trials 1290 (1800) (Psychotic deterioration of epilepsy originally due to war head injury, not guilty by reason of insanity), *Rex v Thomas Bowler*, Annual Register, 309 (1812) (convicted), *Rex v John Boss*, 16 Cr App R 71 (1921) (conviction affirmed), *Rex v Fryer*, 24 Cox C C 403 (1915) (guilty but insane), *Rex v Henry Perry*, 14 Cr App R 48 (1919) (conviction affirmed, the epileptic state must have been operative at the time of the act in such way as to destroy mental responsibility), Berkeley-Hill and Owen, Post-Epileptic Automatism as a Defence in a Case of Murder, Jr Royal Army Med Corps, 1930, iv, 54 (acquitted).

American cases *Commonwealth v Snyder*, 224 Pa 526, 73 Atl 910 (1909) (conviction affirmed, mere fact that accused was an epileptic creates no presumption of insanity or mental irresponsibility), *People v Barberi*, 47 N Y S 168, 12 N Y Cr R 89, 423 (1896) (trial court charge epilepsy must have been operative at time of act in such way as to destroy mental responsibility of defendant at time he acted), *People v Magnus*, 155 N Y S 1013, 92 Misc Rep 80, 34 N Y Cr R 1 (1915) (conviction reversed because undisputed medical testimony showed act was committed during epileptic seizure), *Oborn v State*, 143 Wis 249, 126 N W 737 (1910), 31 L R A (N S) 966 (conviction affirmed mere proof of epilepsy is not proof of insanity).

See, also *Olden v State*, 176 Ala 6, 58 So 307 (1912), *People v Tucker*, 11 Cal (2d) 271, 78 P (2d) 1136 (1938), *Taylor v United States*, 7 App (D C) 27 (1895), *Quatlibaum v State*, 119 Ga 433, 46 S E 677 (1904), *State v Wright*, 112 Iowa 436, 84 N W 541 (1900), *Roop v Commonwealth*, 201 Ky 828, 258 S W 667 (1924), *State v Klinger* 46 Mo 224 (1870), appeal dism'd, 13 Wall 257, 20 L Ed 635 (1871), *State v Hayes*, 16 Mo App 560 (1885), *State v Pennington*, 146 Mo 27, 47 S W 799 (1898), *State v Maioni*, 78 N J Law 339, 74 Atl 526 (1909), 20 Ann Cas 204, *State v Ehlers*, 98 N J Law 236, 119 Atl 15 (1922), 25 A L R 999, *People v Furlong*, 187 N Y 198, 79 N E 978 (1907), *Coffey v State* 60 Tex Cr R 73, 131 S W 216 (1910), *Zimmerman v State*, 85 Tex Cr R 630 215 S W 101 (1919), *Batchan v State*, 104 Tex Cr R 398, 284 S W 549 (1926), *State v Clark*, 156 Wash 47, 286 Pac 69 (1930).

risk of bodily injury (provocation tests) for the purpose of making the latent epilepsy patent, so that diagnostic tracings of the peculiar brain waves may be recorded by the electro-encephalogram (See accompanying illustration)

The second question cannot be answered conclusively in this way, even though the presence of true epilepsy be so established This is because epi-

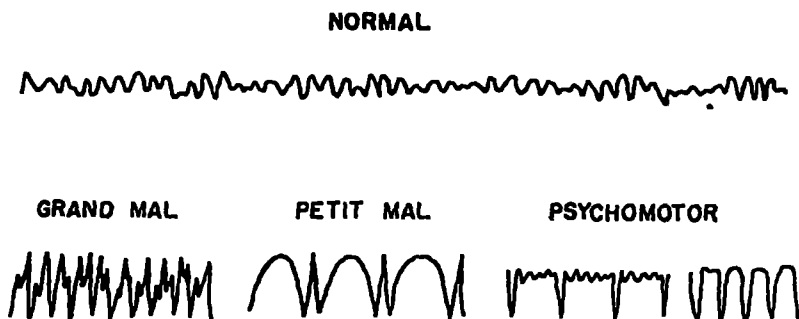


FIG 1 These EEG tracings, made in the laboratory of Lennox and Gibbs, show the types of cerebral dysrhythmia found in three types of epileptic seizures The upper line shows the brain wave pattern of a normal person, the waves occurring at the rate of 8 or 10 a second During a grand mal seizure (convulsive or so-called Jacksonian type), the brain waves become fast and spiky During a petit mal seizure (transient loss of consciousness without generalized convulsions), the brain waves exhibit a wave and spike pattern (Lower middle) During a psychic variant (psychomotor) seizure, the EEG tracing shows slow waves (Lower right)

leptics are orientated and mentally responsible in the interim periods and seizures may be separated by long intervals⁴⁹

It is characteristic of genuine "epileptic" crimes during states of automatism that the actor has an amnesia, or loss of memory, for most or all of the transaction One must investigate every circumstance of the crime and weigh every shred of evidence Usually such crimes are violent or brutal, sometimes they are spontaneous, but craftiness may be used Often the act is committed without plausible motive, often against a loved one rather than an enemy, and there is lack of caution as to the time, place or means taken to avoid detection Some of these indicia of a genuine epileptic crime may be missing If one can show that the amnesia (i e, apparent loss of memory) is simulated, not genuine, this is persuasive evidence that the defendant's whole version of "automatic conduct" is sheer fabrication⁵⁰

⁴⁹ The reader must not assume that all epileptics are likely to commit crimes The writer doubts the authenticity of the "epileptic mechanism" in many cases from medical literature Dr H Houston Merritt, with whom the author has been surveying medico-legal aspects of epilepsy, has followed thousands of epileptics in the clinic and believes that criminal conduct among these persons is a rare phenomenon

This is the belief, also, of Dr Winfred Overholser, well-known forensic psychiatrist (Personal communication)

Dr A Warren Stearns, one of our widely experienced forensic experts, has come to the conclusion that most alleged epileptic "amnesia" is simulated (Personal communication)

It is interesting to note that Ernst in studying etiology of crime in violent criminals concluded that epilepsy was an infrequent factor Ernst, *Ueber Gewalttätigkeitsverbrecher und Ihre Nachkommen* (Violent Criminals and Their Offspring) (1938)

⁵⁰ *Lennox, Amnesia, Real and Feigned, *Am Jr Psychiat*, 1943, 100, 20 U Chi L Rev (April 1943) —

Recently the electro-encephalogram has been used in England in two murder trials involving the defense of epilepsy. The prisoner had not experienced convulsive seizures in prison while under surveillance. The electro-encephalogram, however, proved conclusively that he had the disease, and this corroborative evidence, coupled with other proof, caused the jury to return a verdict of "guilty, but insane" ⁵¹

We may expect to see the electro-encephalogram (E E G) used increasingly in murder trials in an effort to buttress a plea of insanity by showing the prisoner has grossly abnormal brain waves. Courts must be careful not to permit extravagant claims founded upon uncritical interpretation, for cerebral dysrhythmia is a symptom, and medical science is not yet ready to say what every given tracing implies ⁵²

There are other developments in prospect in the field of Medical Criminology. The American Prison Association is working toward adoption of uniform classifications in studying mental defects of prisoners and the diseases they may show ⁵³. More adequate methodology will be devised, and with the eventual advent of centralized statistics, comparative data on the relationship of disease to crime will be available. More voluminous court statistics and special studies by competent medical men or social workers will narrow the gap of inference by providing trustworthy reconstructions of the causes of the particular crime, after the fashion of East's able example. The surge may move forward to the realization of a profession of medical penology with the opportunities and compensation desirable to attract the ablest men ⁵⁴. In that day we shall see more careful thought given to segregation of prisoners according to behavior patterns, and their likely interactions, and we shall see the device of parole used more effectually. We shall see, too, far more attention given to early discovery of pre-delinquency and of potentially dangerous psychopathic personalities so that proper mechanisms for preventing crime can be put into operation ⁵⁵

Medicine made a weighty contribution to the study of human behavior by giving investigators the "case method" ⁵⁶. There is reason to feel that the medical man will continue his substantial part in the study of the thorny practical problems of criminology and sociology.

II FORENSIC PATHOLOGY AND SOME OF ITS OUTSTANDING PROBLEMS

This second great species of Scientific Proof makes use of the fact that most diseases, injuries, and irritants produce characteristic changes in the

⁵¹ Middle Templar, *From an English Office Window*, (Nov 1942) 20 Can B Rev 794 798

⁵² Lennox and Gibbs propose to study amnesic cases and other select groups in prison populations with the E E G to see what may be discovered regarding abnormal brain waves (Personal communication)

⁵³ Personal communication

⁵⁴ Roche, *The Pennsylvania Plan (Intramural Training in Penal-Psychiatry)* (1939) Proc Am Prison Ass'n, 315

⁵⁵ See Thom, *supra*, note 37

⁵⁶ Dr William Healy is generally credited with bringing the individual case method into prominence in the study of crime

tissues of the organs or structures affected This diagnostic change may be discovered by gross inspection at times, or it may call for preparation of tissue sections, embedded in paraffin blocks, cut into thin slices by a microtome, mounted on slides and so stained as to bring out architectural patterns for study under the microscope Pathology, or the morphology of body tissues changed by disease, injury, or irritation, has long been a foundation subject of the medical curriculum The forensic pathologist, ideally, is a medical man who has specialized in Pathology in hospital practice until he is able to diagnose apparent cause of death due to disease He then has acquired knowledge of those many special technics which enable a proper expert to estimate the time of death, to infer the type of weapon used, to distinguish suicide from homicide, in short, to aid the administration of criminal justice by an expert opinion regarding "how, when and by what means the decedent came to his death or injury" ⁵⁷

Most of these studies presuppose a postmortem examination of a dead body Actually the contribution of forensic pathology includes a wide range of clinical and laboratory tests Properly drawn laws would call this science into broader play in non-fatal injuries or accidents

Who, for instance, is apt to have a more reliable grasp of the relationship of trauma to disease than the pathologist? ⁵⁸ In many medico-legal cases in which the nature of a disease is in doubt, we turn to the pathologist to find the answer by studying a lymph node or other bit of tissue invaded by the disease This diagnostic specimen is obtained by the virtually riskless expedient of removing a sample of test material from the patient by the minor procedure known as "biopsy" The probative value of such evidence is so high that in all those usual cases in which the surgical risk is trivial, persons who claim to suffer from cancer as a result of injury probably should be required to submit to diagnostic biopsy as a reasonable requirement of proving the disease

Forensic pathology, as a science, is capable of making at least three, and perhaps more, significant contributions to the problem of proof

- (1) Identification of persons
- (2) Identification of cause and time of death, or of a non-fatal injury
- (3) Causation pathogenesis of the abnormal bodily state or the disease in litigation, including possibility that a given injury caused the terminal condition for which compensation is sought

Example Identification of persons Mr X, a wealthy 68 year old man, suddenly disappeared Problems involving inheritance of property made it material to determine whether his body was that all but destroyed in a fire which also took the life of one John Doe Analysis of blood from the heart showed that the individual had been drinking alcohol Advanced arteriosclerosis showed he must have been an elderly

⁵⁷ The Medical Examiner's Office in New York City and the Department of Legal Medicine in the Harvard Medical School are equipped to give theoretical and applied training to select candidates in this important new profession

⁵⁸ The pathologist is able by virtue of his training and the technics at his command, to study progressive tissue reactions which follow single or repeated traumatic stimuli

peison, as did senile bony changes in the vertebrae and pronounced enlargement of the lateral lobes of the prostate. There was pronounced spondylitis deformans with moderate kyphosis of the upper thoracic spine. There were evidences of an old vascular accident to be seen near the internal capsule in the right lenticulostriate nucleus of the brain. Investigation showed that X suffered from curvature of the spine, had difficulty in passing his urine, a trouble compatible with prostatic obstruction, that three years previously a "stroke" had partially paralyzed his left side, and that he was often given to drinking alcoholic beverages with John Doe. This evidence, coupled with a few other circumstances, was sufficient to satisfy all interested persons that the charred remains were those of Mr. X.⁵⁹

At the moment forensic pathology is highly developed in some quarters as a scientific pursuit, but its proper application is crippled by the fact that its legal utilization is through the antiquated coroner's office. In seven of our American jurisdictions modern medical examiner systems have been established by law.⁶⁰ These are not identical, but under the ideal mechanism, approached in New York City, the forensic pathologist gains paramount right of investigation in a broad category of cases in which death has resulted from accident, casualty, or under unusual or suspicious circumstances. He is able to move forward with alacrity, to take charge of the body and the perishable evidence in the environment, and to give numberless scientific aids to investigating police officers.

In 41 American states and in England, the Coroner's office is still used to investigate such cases. In England since 1926 only medical men or lawyers are eligible to serve as Coroners. In the United States, this official is usually a layman, not infrequently simultaneously holding the office of justice of the peace. The lay Coroner cannot personally perform those scientific duties of investigation which his office requires, and decisive scientific evidence is often lost through delay or oversight. The status of the Coroner, as a quasi-judicial officer, has been anomalous and abortive since the office was first conceived, perhaps as early as the time of King Alfred. The Coroner functions by holding an inquest, and usually must impanel a jury. The verdict of the Coroner or of his jury is of no real legal consequence, for it cannot be offered in evidence in a subsequent prosecution for homicide⁶¹ or in an independent civil action brought on an insurance policy, where "suicide or natural death" might be a controlling issue.⁶² Even Shakespeare made caustic reference to "Crownor's Quest Law."⁶³

⁵⁹ Case of Dr. Alan Richards Moritz, Professor of Legal Medicine, Harvard Medical School.

Following the tragic Cocoanut Grove fire in Boston (Nov. 1942) medical examiners were confronted with the task of identifying scores of charred bodies. Their ability to do this within a very brief period of time was an amazing feat. Certain women burned beyond recognition were successfully identified by the length of time they had been pregnant.

⁶⁰ Massachusetts, New York City, Newark, New Jersey, Maine, Maryland, Connecticut, Rhode Island.

⁶¹ *Blackwell v. State*, 166 Miss. 524, 146 So. 628 (1933), *Hall v. State*, 137 Ala. 44, 34 So. 680 (1903), *State v. McCausland*, 82 W. Va. 525, 96 S. E. 938 (1918), *Hedger v. State*, 144 Wis. 279, 128 N. W. 80 (1910).

⁶² *Boehme v. Sovereign Camp, IV O. W.*, 98 Tex. 376, 84 S. W. 422 (1905).

⁶³ *Hamlet*, Act V, Scene 1, the grave-diggers scene.

It is surprising that we have not brought the important science of Forensic Pathology into more extensive use, for many vital civil and criminal law questions turn upon the fact and circumstances of death, and historically investigation of death was one of the first law-medicine cooperations to be accented ⁶⁴

Without much more ignominious delay, doctors and lawyers must push forward to an ideal "medical examiner act" in each state. Today the Coroner's jurisdiction is narrow and perilous, for if he orders a post-mortem examination in any case except where he has reasonable grounds to suspect

⁶⁴ The Egyptians required physical examination of a woman for pregnancy before she was punished by whipping

In *Ariston v Conon*, an action for assault and battery in Greek law, the plaintiff, who had been badly beaten by defendant, offered testimony of a surgeon to support his claim that "if a sudden discharge of blood had not relieved me at the moment of intense suffering and danger, I should have died of suppuration." The Orations of Demosthenes. The Oration against Conon, Demosthenes, Vol 5, 169 (tr by Kennedy, 1881)

The Romans exhibited the bodies of slain persons in the market place for the populace to view. They also relied upon non-combustibility of the heart to prove death by poisoning.

The "Mirror of Justice," Book 1, c 3 (Selden Society Publication), a source of doubtful authority, refers the institution of the coroner's office to the time of King Alfred.

In the Saga of Njal (an Icelandic saga of events occurring toward the end of the 1100s), we read "I summon these nine neighbors who dwell nearest the spot to ride to the Althing, and to sit on an inquest to find whether Flosi, Thord's son, wounded Helgi, Njal's son, with a brain, or body, or marrow wound, which proved a death wound, and from which Helgi got his death." Dasent, *The Njals Saga* (Edinburgh) (1861)

The "Hsi Yuan Lu" or "Instructions to Coroners," written during the reign Shun Yu (A D 1241-1253), and modified from one generation to another, is still used by Chinese officials in the investigation of sudden death. This curious, notable for its shrewd suggestions, has now been translated into English. See MacAlister, (1924) 17 Proceedings of the Royal Society of Medicine, History of Medicine Section.

Just prior to 1300 A D, the law school at Bologna prevailed upon doctors to open dead bodies in order to determine the cause of death in medico-legal cases. This proved so useful an adjunct to administration of law that the practice of forensic pathology became fairly prevalent. It was then seen that the methods developed could be applied extensively to the independent study of disease and causation of death in cases which had no medico-legal import. Thus the law was the father of forensic pathology and the grandfather of orthodox pathology.

The Borgia family (1476-1519) and the De Medici's (1389-1589) made it a custom to have their physicians examine friends who had died, to make sure that they had not been poisoned.

The "Bamberger Halsgerichtsordnung" (Bambergensis), composed by Johann von Schwartzenberg and enacted by Bishop Georg, in Germany, in 1507, was primarily a statute dealing with criminal procedure. It is interesting to us because it gave physicians and surgeons important functions in the investigation of sudden death, including suspected infanticide, and was the pattern for the more ambitious "Caroli constitutio criminalis" or Carolinian code of Charles V, promulgated in 1532.

See Ludovic, *Constt Crim Car V, Halle* (1716), which gives comparative provisions of the Bambergensis and Carolinian codes. See, also, Von Bar, *History of Continental Criminal Law* (1916), p 208.

For a translation with comments, see *Polsky and Beresford, *Some Probative Aspects of the Early Germanic Codes, Carolina and Bambergensis*, *ANN INT MED* (May 1943), xviii, 23 B U L Rev (April 1943) —

For the history of Forensic Pathology and Institutes of Legal Medicine on the continent, see *The Rockefeller Foundation, Methods and Problems of Medical Education* (9th Ser.), *Institutes of Legal Medicine* (1928)

For papers in this series on Forensic Pathology, see

*Jetter, *Pathological Diagnosis of Causes of Death in an Unselected Series of Acute and Chronic Alcoholics*, *ANN INT MED*, 1943, xviii, —, — *Rocky Mt L Rev* —

*Leary, *How a Modern Medical Examiner's Office Functions in a Typical Investigation of "Sudden Death"* *Points of Superiority Over Coroner's Office*, *ANN INT MED*, 1943, xviii, —

death by criminal violence, he is liable in damages to the next of kin for wrongful autopsy⁶⁵ Tomorrow, the medical examiner will be given a broad discretion as to those fatal or non-fatal cases which he might investigate in aid of criminal or civil litigation Already many of our Workmen's Compensation Acts empower Commissioners to order autopsies where the cause of death is obscure and further light is needed to determine compensability of an alleged injury Courts of those states which refuse a defendant, in personal injury litigation, the right to have the plaintiff examined by an impartial physician appointed by the judge, nevertheless recognize the right of the court, without any empowering statute, to order an exhumation and autopsy of a dead person to provide desirable evidence in a trial for murder⁶⁶

An efficiently operated medical examiner system need not cost substantially more than the coroner's office Probably the desirable goal is a compact organization of forensic pathologists, financed as a state agency, with stations in a few metropolitan centers, so that the staff could serve as consultants in obscure cases Ordinary cases of sudden death could be passed upon by local physicians Such a medical examiner's office could maintain a functional cooperation with a state Scientific Crime Detection Laboratory, as both agencies are auxiliary aids to police and law enforcement agencies

III SCIENTIFIC CRIME DETECTION

Scientific Proof has manifold applications in detecting criminals and reconstructing essential evidence of the corpus delicti or body of the crime The reader is saved from surfeit by limitations of space, but perhaps I can cajole the intellectually curious to scan a few select items, presented in chronological form, to show how broad and deep are the implications of scientific crime detection

- 1 2030 B C *Trial by ordeal* The Code of Hammurabi⁶⁷ mentioned ordeals, and the ordeals of fire, water and the like were widely practiced to determine guilt or innocence They were not abolished in England until 1213⁶⁸ Now recognized as superstition, at the time of their use they were regarded as objective scientific corroboration They reflect the constant questing for proof by external tests

In primitive India, the Hindu priests required one suspected of crime to chew dry rice for a given time and then to eject the *bolus* upon a piece of dry bark If the rice was still dry, the suspect was guilty This had a pseudoscientific rationale, it was believed that fear of detection and punishment would inhibit the nervous mechanism of the salivary gland and prevent the flow of saliva⁶⁹

⁶⁵ *Aetna Casualty and Surety Co et al v Love*, 132 Tex 280, 121 S W (2d) 986 (1938) Liable for ordering post-mortem examination to determine cause of obscure death in aid of workmen's compensation insurance investigation *Gurganious v Simpson*, 213 N C 613, 197 S E 163 (1938) Liable for autopsy on boy drowned in Y M C A pool, there being no suspicion of foul play

⁶⁶ *Gray v State*, 55 Tex Cr R 90, 114 S W 635 (1908)

⁶⁷ Thatcher, *The Library of Original Sources*, Vol I, p 439

⁶⁸ See Watt, *The Law's Lumber Room*, (2d ed) London (1898), Lea, *Superstition and Force*, (4th ed) Phila (1892)

⁶⁹ Glaister, *The History of Medical Jurisprudence and Criminal Procedure in Primitive and Mediaeval Times* (1897) *The Medical Times and Hospital Gazette*

- 2 c 1,000 B C *Proof of perjury and paternity by forensic psychology* The Judgment of Solomon as to which of two female claimants was the true mother of the child in question was based on their psychological reactions to the proposal that the child be divided in two ⁷⁰
- 3 600 B C–500 A D (*The Talmud*) *Scientific disproof of adultery* A husband, desiring to divorce his wife, contrived to get her and other guests drunk at a party, carried her and a male guest to a couch, and threw egg albumen between them. He then called neighbors to bear witness to adultery. The resourceful wife, on becoming sober, summoned her physician, who identified the substance as egg white, not seminal fluid. We are not told what means he used. (Today, we would use specific chemical tests such as the Florence test,⁷¹ or the microscope, or immunological methods.)
- 4 287–212 B C *Proof of adulteration of metal* Legend has it that Archimedes, the Greek physicist and mathematician, used scientific proof to settle an issue involving possible adulteration of metal and obtaining of money under false pretenses. Heiron called upon Archimedes to say whether the suspected smith had used silver alloy in a gold crown. While taking a bath, Archimedes conceived the idea of immersing the crown in water to see how much liquid it displaced as compared with true gold. With real scientific independence and ardor, he sprang from the bath, and ran naked through the street to his home shouting "Eureka!" ⁷²
- 5 15 B C–19 A D *Forensic chemistry toxicology non-combustibility of the heart as proof of death by poisoning* The ancients falsely believed that non-combustibility of the heart was proof of poisoning. This assumption was challenged by defense counsel in the trial of Plandina, wife of Piso, for the murder of Germanicus. The defense admitted that the heart of Germanicus was non-combustible, but claimed this was due to heart disease. Collateral evidence leads us to believe that Germanicus probably did die of natural causes ⁷³
- 6 c 1591 *Forensic microscopy* Hans and Zacharias Jansen invented the microscope ⁷⁴. But we may point out that the history of lenses runs back to the Egyp-

⁷⁰ First Kings, III, 16

⁷¹ Florence, 10 Arch d'Anthrop Crim 417 (1896) The alleged seminal stain is put into solution, a drop is placed on a glass slide and allowed to nearly dry, a drop of Florence's solution (potassium iodide 15 grams, iodine 25 grams, and water 30 cc) is added, and the preparation is viewed at once under the microscope. If semen is present haemin-like crystals form, singly, in clusters and in rosettes and soon become unrecognizable. The test is not absolutely specific as the positive reaction is produced by action of iodine on choline, a natural base which occurs in many cells. It is most valuable as a negative test. Recently Pollak has canvassed all the useful methods of identification. Pollak, Semen and Seminal Stains, A Review of Methods Used in Medico-Legal Investigations, Arch Path, 1943, xxxv, 140

⁷² Heath, Archimedes, London (1920)

⁷³ Comments of the ancient writers on this case are interesting

Suetonius, Twelve Caesars, Caligula, 1 "[Germanicus] died of a lingering disorder not without suspicion of being poisoned, for besides the livid spots which appeared all over his body, foam poured from his mouth, and also his heart was found uncharred amongst the bones, its nature being such, as it is supposed, that when tainted by poison, it is indestructible by fire."

Tacitus, Annales, Book 2, Sec 73 "His body, before its commitment to the pile, was exhibited naked in the Forum of Antioch, the place fixed upon for the sepulchral rites. Whether it bore the marks of poison remained undecided, for people were divided in their conclusions according as they pitied Germanicus and presumed the guilt of Piso, or were prejudiced in his favor."

Pliny, Natural History, XI, 37, Sec 71 "It is denied that one can cremate those who have died of a cardiac illness, and those who have taken poison. There surely survives an oration of Vitellius in which he charges Gnaeus Piso with this crime on this ground that it had been witnessed that the heart of Germanicus Caesar could not be cremated because of poison. Piso was defended as to the nature of the illness."

⁷⁴ Clay and Court, The History of the Microscope, London (1932)

- tians, and that Leonard Digges, c 1550, had employed a telescope to view far-off objects ⁷⁵
- 7 1727 *Forensic photography* Johann Heinrich Schulze (1687-1744), a physician of Halle, placed objects in a glass containing a mixture of white chalk and nitrate of silver and by exposing them to light produced transient photographic images, the first ever achieved ⁷⁶
 - 8 1800 *Forensic physics* F W Herschel discovered infra-red rays
 - 9 1804 *Forensic physics* J W Ritter discovered ultra-violet light which is now used for preliminary identification of stains, for showing up obliterated writing in forgery, etc ⁷⁷
 - 10 1829 Sir Robert Peel introduced the Act in Parliament which established a police system for London
 - 11 1836 *Forensic chemistry toxicology* James Marsh (1794-1846), English chemist, described his famous "Marsh test" for identifying minute traces of arsenic, the basis for later, more refined tests ⁷⁸
 - 12 1858 *Personal identification fingerprints* Sir William Herschel introduced fingerprinting as the official system of individual identification in India ⁷⁹
 - 13 1860 *Forensic physics spectrographic analysis* Kirchhoff and Bunsen noted that when temperature of a gas is raised sufficiently it radiates light or energy of characteristic wave lengths dependent on the molecular structure of the gas tested and the method of excitation ⁸⁰ These line spectra enable identification of inorganic substances which can be vaporized The heat required for vaporization usually destroys organic substances
 - 14 1879 *Personal identification* The Bertillon Cabinet was founded in Paris The anthropological identification method of Alphonse Bertillon (1853-1914) was

⁷⁵ Digges, T, *Pantometria* (1571), p 5 of preface, says of his father, Leonard Digges

"My father, by his continual paynfull practices assisted with demonstrations mathematicall, was able, and sundrie times hath, by proportionall glasses, duely situate in convenient angles, not onely discovered things farre off, read letters, numbred peeces of money with the very coyne and superscription thereof, cast by some of his freends of purpose uppon Downes in the open fieldes, but also seven myles off declared what hath been doon at that instante in private places"

⁷⁶ Stenger, *The History of Photography*, Easton, Pa (1939) First permanent photograph J Nicephore Niepce (1822), Daguerrotype perfected Daguerre and Niepce (1839) For Forensic Photography, see Scott, *Photographic Evidence*, Kansas City (1942)

⁷⁷ Nicholson's Journal (1804), 214 See Ellis and Wells, *The Chemical Action of Ultra-violet Rays* (Revised by Heyroth), N Y. (1941), also, Radley and Grant, *Fluorescence Analysis in Ultra-violet Light* (2d ed) London (1935), also, Rorimer, *Ultra-violet Rays and Their Use in the Examination of Works of Art*, N Y (1931)

Wheatstone in 1835 was probably the first to observe that a brilliant light (ultra-violet light) is emitted when mercury is vaporized in an electric arc Perkin, (1911) 6 Trans Faraday Soc 199

⁷⁸ Edinburgh Philosophical Journal (Oct 1836)

See *Wigmore, *Circumstantial Evidence in Poison Cases*, Clinics, 1943, II, 1507, 23 B U L Rev (April 1943) —

*Walker, *Scientific Evidence in Poisoning Cases*, Clinics, 1943 II, 1520, 23 B U L Rev (April 1943) —

*Thayer, *Note on Poison in Roman Private Law*, Clinics, 1943, II, 1625, 23 B U L Rev (April 1943) —

Mathieu Joseph Bonaventure Orfila (1787-1853), French toxicologist and chemist, born in Spain, is regarded as the father of scientific toxicology He published his *Traite des poisons, or Toxicologie generale*, in 1813

⁷⁹ Mitchell, *The Scientific Detective and the Expert Witness*, N Y (1931) For one of the best resumes of the scientific and legal history of fingerprints, see Hankison, *Evidence of Finger-Prints*, ch 54 in *Underhill's Criminal Evidence* (4th ed by Niblack), Indianapolis (1935)

⁸⁰ Pogg Ann, (1860) 110 160, (1861) 113, 337 See Wilson *Spectrographic Analysis as an Aid in Identification Problems*, (1934) 25 J Crim L and Crim 160

- officially adopted in France in 1888 as a means of identifying criminals, but it was later abandoned with advent of finger-printing⁸¹
- 15 1893 *Scientific crime investigation* Hans Gross, sometimes called "the father of scientific criminology," brought out his classic treatise⁸²
 - 16 1895 *Forensic physics Roentgen-ray* Professor Wilhelm Konrad Rontgen of Wurzburg, Bavaria, discovered that when cathode rays encounter matter, they give off secondary rays which carry no charge but penetrate ordinary solids⁸³
 - 17 1898 *Forensic anthropology Pearson's formula* Kail Pearson, on June 16, 1898, in a paper read before the Royal Society, announced his formula for reconstructing the stature of a corpse or living person from such bones as the femur, humerus, radius and tibia⁸⁴
 - 18 1900 *Forensic immunology identification by human blood groups* Landsteiner made the first observations regarding differences between bloods of normal human beings⁸⁵ This ushered in the important blood grouping determinations, primarily useful as evidence of non-paternity⁸⁶
 - 19 1901 *Forensic immunology and biochemistry the precipitin test* Uhlenhuth showed that due to protein specificity, an unknown blood can be identified as of human or animal origin by utilizing principles of immunology described by Boidet in 1898 (The source of any minute amount of protein may be identified in the same way) Uhlenhuth was the first worker to publish results of tests demonstrating practical application of the precipitin reaction to medico-legal work Having injected rabbits with human blood he used the antiserum so produced in tests against 19 different bloods and found that a positive precipitin reaction occurred only with human blood He also used the method to identify human blood on test objects such as a stick, sand, cotton trousers, a hatchet, and several stained articles⁸⁷
 - 20 1912 *Forensic physics Fire-arms identification* Balthazard photographed bullets and from the photographic enlargements identified the precise weapons from

⁸¹ For a full description of the Bertillon method, see Bertillon, *Identification of the Living* (tr by Webster) in 1 Peterson, Haines and Webster, *Legal Medicine and Toxicology*, (2d ed 1923) Phila

⁸² Gross, *Handbuch fur Untersuchungsrichter, als System der Kriminalistik* (2 vols 1893), translated into eight foreign languages, in English under the title, *Criminal Investigation, a Practical Textbook for Magistrates, Police Officers and Lawyers* (by John Adam and J Collyer Adam, 3d ed by Norman Kendal, London, 1934)

⁸³ 6 L'Éclair Elect 241 (1896) Rontgen's three memoirs are translated in *The Electrician* (Jan 24, 1896, and April 24, 1897) Roentgen-ray evidence, because of its direct visual quality, was speedily admitted by the courts (*Smith v Grant* (1896), 29 Chicago Legal News 145)

⁸⁴ Pearson, *On the Reconstruction of the Stature of Prehistoric Races*, (1898) 192 *Philosophical Trans of the Royal Society*, Ser A, 169 His calculations were based in part upon the measurements of Rollet at Lyon in 1889

See *Hooton, *Medico-Legal Aspects of Anthropology*, Clinics, 1943, 11, 1612, 15 Rocky Mt L Rev (April 1943) —

⁸⁵ Landsteiner, K *Zentralbl f Bakt, Parasitenk u Infektionskrankh*, 1900, xxvii, 357
⁸⁶ See *Boyd, *Protecting the Evidentiary Value of Blood Group Determinations*, Clinics, 1943, 11, 1536, 17 So Cal L Rev (March 1943) —

*Maguire, *A Survey of Blood Group Decisions and Legislation in the American Law of Evidence*, Clinics, 1943, 11, 1560, 17 So Cal L Rev (March 1943) —

*Schoch, *Determination of Paternity by Blood Grouping Tests The European Experience*, Clinics, 1943, 11, —, 17 So Cal L Rev (March 1943) —

⁸⁷ Uhlenhuth *Deutsch med Wchnschr*, 1901, xxxvii For practical details of this test, see Smith, S. and Glaister, J., *Recent Advances in Forensic Medicine*, Phila (1931), 99

The precipitin test was first used in a murder trial in 1902 in France, to prove that stains on the prisoner's clothes were human blood and not rabbit's blood, as he claimed It was first used in an English court in 1910 in the murder trial of Marke Wilde Dr Willcox testified that old stains on the blue serge coat of the prisoner gave a positive precipitin test for human blood

which they had been fired. He did this by comparing the markings made on bullets with those on other test bullets fired from the suspected weapons⁸⁸

- 21 1912-1930 *Identification of instruments by markings* Luke S May carried on extensive studies devoted to identification of knives, tools and instruments by photo-micrographs of scratches and marks made in their use⁸⁹
- 22 1921 *Lie detector* Larson began work on deception tests. He constructed a portable "polygraph" for recording relative changes in pulse, blood pressure and respiration. The so-called guilt reaction, due to anxiety, produces physiological changes in these values. Larson also developed an improved technic of questioning the suspect⁹⁰
- 23 1923 *Identification preserving imprints by moulage methods* Hans Müllner of Graz reported his quick method of making casts of impressions left in soft materials⁹¹
- 24 1925 *Ballistics comparison microscope* The comparison microscope was devised by Gravelle of South Orange, N J, at the instance of Calvin Goddard and was put to use in the Chicago Scientific Crime Detection Laboratory established in 1929⁹². It enables convenient microscopic comparison of two objects, such as markings on the death bullet and those on a test bullet fired from the gun which the prosecution alleges to have been the weapon used
- 25 1929 *Analysis of dust traces* Considerable credit should be given to Edmund Locard, able director of the Laboratory of Police Technique of Lyon, France, for his valuable and refined work on this subject. Dust analysis had been faintly alluded to by old writers on legal medicine, and was actually applied by Hans Gross, but it was most stressed by Conan Doyle as a favorite method of his detective, Sherlock Holmes in such stories as "A Study in Scarlet," "The Five Orange Pips," and "The Sign of the Four". Locard attributes his original interest in the subject to reading the exploits of Sherlock Holmes⁹³
- 26 1932 The Federal Bureau of Investigation (U S Department of Justice) established its Scientific Crime Detection Laboratory
- 27 1932 *Blood alcohol level as evidence of intoxication* Widmark in Sweden showed by experimental work that blood alcohol determinations are valuable indices of intoxication⁹⁴. This work led to adoption in Sweden of compulsory blood tests in criminal cases and traffic accidents. Traffic officers are equipped to take blood samples and these are sent to the State University of Lund for analysis

⁸⁸ Goddard, *Arms Identification Its Story*, (Nov 1935) 10 *Police* "13-13" 10

⁸⁹ May, *Identification of Knives, Tools and Instruments a Positive Science*, (1930) 1 *Am J Police Science* 246. Metallographic analysis was approved in *Magnuson v State*, 187 Wis 122, 203 N W 749 (1925), one of the most remarkable cases of scientific crime detection to be found in the law reports

⁹⁰ Trovillo, *A History of Lie Detection*, (1939) 29 *J Crim L and Crim* 848. See, also Larson, *Lying and Its Detection*, Chicago (1932), Inbau, *Lie Detection and Criminal Interrogation*, Balt (1942)

For applied use in State Police work, see *Snyder, *Criminal Interrogation with the Lie Detector (Eight Years' Experience by the Michigan State Police)*, *Ann Int Med*, 1943, viii, 551, 15 *Rocky Mt L Rev* (April 1943) —

⁹¹ Müllner, 4 *Kriminalistische Monatshefte*, (No 12) 1930. Transl 23 *J Crim L & Crim* (1932-3) 351

⁹² Goddard, *Crime Detection Laboratories in Europe*, (1930) 1 *Am J Police Science* 13, at page 21

⁹³ (1929) 4-5 *Revue Internationale de Criminalistique*, 176-249. Transl (1930) 1 *Am J Police Science* 276, 401, 496

⁹⁴ See Widmark, *Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung*, Berlin, Urban & Schwarzenberg, 1932

For practical aspects see *Ladd and Gibson, *Legal-Medical Aspects of Blood Tests to Determine Intoxication*, *Ann Int Med*, 1943, viii, 564, 29 *Va L Rev* (April 1943) —

It is possible by scientific means to determine from a shattered window pane whether it was broken from the outside or from within the house⁹⁵, to analyze minute traces of soil found on the suspects' shoes⁹⁶, to gain signal help from microscopic preparations of a single hair⁹⁷, to draw valuable inferences from tire and skid marks⁹⁸, to reach a conclusion as to whether a gun-shot wound was inflicted by a weapon fired at a distance or by a gun held pressed against the victim's body⁹⁹

As the reader may have noticed, this species of Scientific Proof has certain special attributes

- (1) Convergence of attention on problems of *identification*,
- (2) Applied use of the principles of the physical sciences,
- (3) Reference of problems involving medical science to independent consultants,
- (4) Chief connections with administration of criminal justice, main legal counterpart in the rules of evidence and the doctrines of criminal law which apply to investigation and trial of criminal charges

Today the Scientific Crime Detection Laboratory of the F B I is carrying on specialized investigations for many of the State Police Forces¹⁰⁰. In time each State Police Force should have its own laboratory, and pains must be taken to make this work a career for the highly trained man, perhaps on some civil service basis. Many of the Scientific Crime Detection Laboratories now scattered throughout this country have limited value because of a tendency to draw personnel from the ranks of police officers on a seniority principle.

IV SCIENTIFIC MODES AND MECHANISMS OF PROOF

Under this head, we may study particular means of acquiring scientific evidence. We may study the critical limitations of such evidence producing

⁹⁵ Matwejeff, *Criminal Investigation of Broken Glass*, (1931) 2 *Am J of Police Science* 148. Tryhorn, *The Examination of Glass*, 12 *Police J (of England)* No 3 (1939), reprinted in (1939) 30 *J Crim Law & Crim* 404.

⁹⁶ Johannsen, *Manual of Petrographic Methods* (1918).

⁹⁷ Glaister, *Hair Considered Medico-Legally*, (1927-8) 22 *Trans Medico-Legal Soc* 95. Kirk, *Human Hair Studies* 1. General Considerations of Hair Individualization and Its Forensic Importance, (1940) 31 *J Crim Law & Crim* 486. See, also, Smith and Glaister, *Recent Advances in Forensic Medicine*, Phila (1931).

⁹⁸ Harper, *A Graphical Method for Rapidly Determining Minimum Vehicle Speeds From Skid Marks*, (1939) 30 *J Crim Law and Crim* 96. Wiener, *An Inaccuracy in the Determination of Vehicle Speeds*, (1940) 31 *J Crim Law and Crim* 249.

⁹⁹ Walker, *Bullet Holes and Chemical Residues in Shooting Cases*, (1940) 31 *J Crim Law and Crim* 497.

For an interesting study in *Forensic Physics*, see Oldenburger, *Human Trajectories*, 13 *J Appl Phys* 460 (July 1942). The author summarizes his results and paper as follows:

"It is proved that a human being M falling from a ledge A through the air to the ground below will attain the greatest range if M falls forward while standing upright. If M was found on the ground at a position B beyond this range of fall, M furnished energy himself to attain B . An analysis of trajectories from A to the ground, due to an effort on the part of M , is given. If the kinetic energy which M must produce to reach B is much greater than that which M can furnish after loss of balance, M made the trip from A to B by a premeditated jump. Such analyses are important for determining suicides."

¹⁰⁰ *Hoover, *The Scientific Crime Detection Laboratory, Clinics*, 1913, II, 1503, 20 *U Chi L Rev* (April 1943) —

agencies as the roentgen-ray,¹⁰¹ the electro-cardiograph,¹⁰² the electroencephalograph,¹⁰³ and the lie detector¹⁰⁴

We may study also the adequacy of existing modes of trial, and of social mechanisms needed to bring scientific evidence to the point of maximum legal utility. I have alluded to the need of taking scientific issues from lay jurors. Professor Edmund Morgan, Reporter of the American Law Institute "Committee on Evidence" charged with developing a new simplified Code of Evidence, has described certain immediate changes which proponents of Scientific Proof should help translate into legislation.¹⁰⁵ Professor Roscoe Pound, known everywhere for his school of sociological jurisprudence, believes that analysis has outrun social synthesis. He proposes a Ministry of Justice as a means of effecting rapid and successful transfusions of scientific thought into the circulating blood stream of law.¹⁰⁶

In times past I have suggested the formation of a National Scientific Commission to serve as a master censor for the courts.¹⁰⁷ Such a body, made up of qualified legal and scientific persons, could probe into the merits of each species of scientific proof and lay down appropriate criteria, safeguards and cross-checks needed to make the evidence trustworthy. The several states could pass statutes providing that scientific evidence which conforms to requirements of the National Scientific Commission is to be admitted as *prima facie* evidence in any legal proceeding in which it is relevant. Such a body could develop also a comprehensive system for certifying the proficiency of expert witnesses.

In respect to every species of expert testimony, there is a need for criteria, defining what is possible, what is impossible, and what is acceptable practice, but their development has been restricted chiefly to problems of identification. It is not uncommon to see "experts" making blood group determinations by such impossible methods as microscopic inspection of dried blood smears. It is not a rare thing to see general practitioners postulating injury as the probable cause of some disease, when current medical science would not accept the evidence relied upon as satisfactory.

Indeed, there is a real danger in the fetching term "Scientific Proof," for it may lead us to overconcentrate on the high probative value of this species of evidence, while glossing over serious dangers which lurk in its use.

¹⁰¹ *Donaldson, Medical Facts that Can or Cannot be Proved by X-Ray, Historical Review and Present Possibilities, *ANN INT MED*, 1943, XVIII, 535, 41 *Mich L Rev* (April 1943) —

¹⁰² *Riseman, Principles of Electrocardiography, 15 *Rocky Mt L Rev* (April 1943) —

¹⁰³ *Smith and Riseman, Applied Use of the Electrocardiograph in Legal Proceedings, 15 *Rocky Mt L Rev* (April 1943) —

¹⁰⁴ See this paper, *supra*, and see *Lennox, Amnesia Real and Feigned, fn 50 *supra*

¹⁰⁵ *Snyder, Criminal Interrogation With the Lie Detector, *ANN INT MED*, 1943 XVIII 551, — *Rocky Mt L Rev* —

¹⁰⁶ *Morgan, Suggested Remedy for Obstructions to Expert Testimony, *Clinics*, 1943, II, 1627, 20 *U Chi L Rev* (April 1943) —

¹⁰⁷ *Pound, A Ministry of Justice As a Means of Making Progress in Medicine Available for Courts and Legislatures, *Clinics*, 1943, II, 1644, 20 *U Chi L Rev* (April 1943) —

¹⁰⁸ Smith, H. W., Cooperation Between Law and Science in Scientific Proof (June 1941) 19 *Tex L Rev* 414

"Scientific Proof" covers a vast range of expert testimony, varying widely in probative value. Certain methods of identification, such as finger-printing, contain only a minute chance of error, either as regards premises employed or actual execution of tests. Next we drop down to such activities as forensic chemistry and blood group work, where premises are scientific, but errors in procedure are more likely. Here there is real risk of mistake if the witness does not have very special qualifications. Handwriting falls a little lower down the scale; Albert S. Osborn has brought this field from art to science, but there is still a component of subjective skill in its application. Forensic Pathology in most particulars holds its own, in probative value, with other trustworthy identification methods. Clinical Forensic Medicine is a blending of science and art, naturally more amenable to method in diagnosis than in prognosis, where facts must be aided by experience and good opinion.

Each species of evidence calls for safeguards and cross-checks, and its own particular criteria of proof, if we are to avoid losing the contribution of science in a welter of opinion. In all those cases in which the proposed expert needs special indoctrination and training, a certificate of proficiency should be required before he is allowed to testify. If evidence is to be founded upon test materials, provision should be made for preservation of this material for independent corroboration studies to settle doubts that might arise in the mind of court or adversary. Lack of any such mechanisms may account for the willingness of courts to say that even if scientific evidence is undisputed, the jury may rely on contrary lay evidence to enter a verdict opposed to the Scientific Proof.¹⁰⁸ Perhaps the particular expert does not look too scientific to the court, perhaps, too, the judge feels that there is no satisfactory cross-examination possible of a complicated procedure. It is well known that most lawyers are not equipped to overthrow this species of evidence, and the danger is enhanced by the fact that a fundamental error may be merged beyond discovery in the standardized routine of a textbook procedure. If the test material were saved, as usually is possible,

¹⁰⁸ In *Arais v Kalenskikoff*, 10 Cal (2d) 428, 74 P (2d) 1043 (1937), 115 A L R 163, scientific evidence based on blood group determinations was uncontradicted that defendant could not be the father of plaintiff's child. The trial court refused to instruct a verdict for defendant and on the strength of lay testimony the jury returned a verdict for plaintiff finding D to be the father of her child. This judgment was affirmed by the California Supreme Court.

In like manner, in *Rev v True*, 127 L T 561 (1922), the Court of Criminal Appeal in England held that a jury was entitled to find that a defendant, under prosecution for murder, was sane at the time he committed the homicide, despite uncontradicted medical testimony to the contrary.

Contra *Schulze v Schulze*, 35 N Y S (2d) 218 (1942). Husband, X, as plaintiff sought a divorce from his wife, Y, defendant, on the ground of adultery. Y contended that child, C, was the offspring of X and that she had not committed adultery. X and Y had been separated for some time, but evidence as to access during the period of separation was conflicting. E, an expert witness, offered uncontradicted testimony that he had performed blood group determinations which showed X could not possibly be the father of C. Held: Though "the presumption of legitimacy of a child" born in wedlock is "one of the strongest presumptions known to law," it is rebutted, and the lay testimony of access overcome by the undisputed scientific evidence of non-paternity. The uncontradicted scientific proof is entitled to control the issues raised.

the trial court could appoint an impartial expert to repeat the procedure or study. If results were consistent, and the scientific evidence were conclusive of the issue, many trial courts would refuse to permit the jury to override such findings.

One result of our present adversary system of trial is that science may be born anew in every lawsuit where two experts disagree. That a scientific principle or finding can be true in A's case and untrue in B's case is squarely opposed to the concept of the universality of scientific truth.¹⁰⁹

In our more progressive states, if the case turns on a scientific question, and expert X gives uncontradicted testimony that the facts are ABC, the trial judge will instruct the jury that they must return a verdict finding the facts to be ABC.¹¹⁰ If, however, expert Y disagrees with expert X, the lay jurors are to say which is the preferable view, or to discard both in favor of lay testimony. These are the mechanisms of procedure and trial.

What would P (a member of the public) think if he experienced the following treatment in a modern hospital?

P goes into hospital suffering pain. Dr. X says (testifies) that the pain is due to heart trouble. No one disputes him and the case is treated as one of heart disease.

Assume, instead, that Dr. Y examines P and says (testifies) that P is suffering from gall-bladder trouble. The hospital superintendent, desiring to resolve the conflict, calls in a layman from the street to say whether Dr. X or Dr. Y is to be believed, and on that basis disposes of P's case.

P would be properly shocked at such a procedure, for he would naturally expect that Dr. Z, an even greater consultant (expert referee), would be called into consultation to determine the true facts.

The reader will note that I press always for the conviction that laymen cannot successfully try scientific issues. The layman is apt to import distorted notions of scientific matters into the judging process, and the warping effect is as pernicious whether he gives excessive weight to the evidence (augmentation) or too little (displacement).¹¹¹ Three cardinal aspects of evi-

¹⁰⁹ There would seem to be two solutions to this jury trial dilemma.

(1) To cover litigation where a scientific finding should control the outcome of the case, and the undisputed scientific evidence points one way, I would suggest a constitutional amendment empowering the trial judge to instruct the jury to return its verdict in accordance with the scientific proof. The reader will understand that now it is constitutionally impossible for judges to direct verdicts of guilty in criminal prosecutions. This is in contrast with the situation in civil litigation where the judge may instruct a verdict if all the credible substantial evidence points one way.

(2) In states where the court has power to appoint an impartial expert, supplementary legislation might be warranted providing that the scientific findings established in the first trial shall be binding in subsequent litigation arising out of the same general transaction. If an impartial referee system be introduced for trial of scientific issues, one might well argue that a finding on full investigation should be given effect against the whole world.

Under our strongly entrenched adversary system, with stress placed on the varying diligence of litigants and counsel, the first solution proposed would be the more acceptable.

¹¹⁰ I think it is safe to say that this is not yet the majority rule.

¹¹¹ A. Augmentation. "Plowden (1519-1584), one of the heroes of jurisprudence, of the growth of the sixteenth century, was a deserter from one of those professions which are built on physical science, he flourished toward the latter part of the reign of Elizabeth. From the report of a cause relative to a mine, he took occasion to unfold to the eyes of his brethren of the long robe the wonders of mineralogy—a terra incognita, as strange to them as America

dence are relevancy, probative value and persuasive value. For a perfectly competent, expert trier of fact, probative value and persuasive value should be the same. The layman naturally cannot grade scientific evidence according to its true probative value, and in consequence he is more convinced by the persuasive or psychological appeal of evidence.¹¹²

Assuming, as we must, that laymen may continue to try scientific issues for a long while to come, is it possible to make criteria of Scientific Proof universally available in the "valuing" process, even where these have not been put in evidence?

Facts not offered in evidence from the witness stand cannot be considered unless they be proper subjects for judicial notice, and so notoriously known that the court may dispense with the formality of their proof. The doctrine of judicial notice may enable appeal courts to tap new and authoritative criteria of Scientific Proof pronounced by leading spokesmen of medicine and the sciences. This would give to such courts a needed measuring rod to determine whether the expert testimony put forward at the trial was sufficient to support the verdict, thus enabling a more delicate valuation than that afforded by the crude "conflict of testimony" test. The chief difficulty here would lie in the judge's consulting the wrong bootblack,¹¹³ but if we are

had been to their immediate progenitors. "The theory of mineralogy," said he, "is to the last degree a simple one. In sulphur and mercury, the Adam and Eve of the mineral creation, the whole tribe of metals behold their common parents. Are they in good health? The two perfect metals, gold and silver, are the fruits of their embrace. Do they labour under any infirmity? The effects of it are seen in the imperfect metals, their imperfect progeny." Bentham, *Rationale of Judicial Evidence* (1827) Vol 1, p 7. And see fn 112 post.

B. *Displacement*. No more striking case could be mentioned than *Mathews v People*, 89 Colo 421, 3 P (2d) 409 (1931). Accused was convicted and sentenced to life imprisonment for having murdered his wife. The vital proof was scientific testimony of a ballistics expert that bullets recovered from the body of decedent were fired from a pistol which defendant admittedly had in his possession continuously. D was a respectable citizen and offered an alibi. On the trial the ballistics expert was allowed to pass the bullets among the jurors who were permitted to look through a hand lens at grooves on the death bullets in determining identity of the pattern with grooves on test bullets fired through the barrel of the recovered pistol. (Proper procedure would have been to use a comparison microscope or to make imprints of the etched grooves by rolling the bullets to be compared over plastic material according to the technique of Moritz.) After the jurors by this dangerously unscientific gross inspection satisfied themselves that the same gun fired both bullets and found accused guilty, members of the appeal court undertook to determine the scientific issue for themselves. The learned members of that tribunal inspected the bullets sent up with the record, admittedly used a different lens from that employed by the jurors, and held that no such grooves were present as would warrant the conviction. On this ground they reversed the judgment. Burke, J said "All these bullets are before us. Each of the justices has examined them under a powerful glass (though not the identical one used at the trial) and has been wholly unable to see anything resembling what the witness says he saw and which he assumed to exhibit to the jurors. This court is as capable of passing upon such evidence as the jurors who heard it. Here the sole evidence of guilt is the assertion that certain alleged markings appear upon these bullets. We examine them and find nothing of the kind. Hence the judgment must necessarily be reversed. The thread is entirely too slender to support a sentence of life imprisonment. The evidence is not only weak and uncertain, it is no evidence."

¹¹² See Smith, *Components of Proof in Legal Proceedings*, (Feb 1942) 51 *Yale L J* 537.

¹¹³ This problem has arisen in malpractice actions filed by patients against their physicians for alleged mismanagement of fracture cases. Some courts have held that failure to employ the roentgen-ray in fracture cases is negligence, and that it is so commonly recognized as such that the court will take judicial notice of the fact even though plaintiff offers no ex-

to continue our present system of trial, this would seem to be a lesser evil than cutting the judge off from any usable erudition in his difficult task of appraising expert testimony. The higher the authority for these scientific criteria, the less the risk and the more easily is the doctrine of judicial notice invoked, and these facts, again, argue for some new official commission, Ministry of Justice, or point of reference.

Jurisprudential Use of the Scientific Rationale In marshalling those ultimate facts which should orientate legal doctrine, model legislation or social policy, science may proffer methods of research, or on occasion the very criteria, for action. A case in point is the legislation authorizing compulsory sexual sterilization. Indiana passed the first statute on March 9, 1907, and up to this moment 30 states in all have enacted such laws. The primary intention of such legislation was eugenic—to prevent carriers of inheritable defects from transmitting them, and thus to protect society from new members pre-destined to insanity, feeble-mindedness or other disabling defect. By vasectomy in case of males, and by tying off the fallopian tube in case of females, specified classes of persons previously committed to state institutions would be rendered safe to reënter society. No one can doubt that sexual sterilization may prove to be a beneficent factor in race eugenics, but it is equally clear that legislative enthusiasm has outrun scientific criticism. This appears from several considerations:

(1) The classifications do not always correspond to diseases recognized as transmissible by heredity. Some statutes set up such categories as "moral degeneracy," a sociological symptom, not a diagnosable medical disease, and not a condition known to be transmitted by inheritance.¹¹⁴

(2) The legislation is not bottomed on medical knowledge regarding "inheritable disease," or scientific regard for the feasibility of spotting recessive carriers of the defect.

(3) The legislation touches such a small percentage of the described classes, and often at so late a date, that the eugenic goals of the legislation cannot be achieved (For instance, only 6 per cent of epileptics are institutionalized).

Dr Abraham Myerson shows most convincingly that legislation which rests upon scientific premises can and must be tested by scientific principles.¹¹⁵ Dr John Rock has expounded the scientific principles which must be taken

pert testimony to prove that the omission in the particular case was a departure from average medical standards in the community. *Whitson v Hillis*, 55 N D 797, 215 N W 480 (1927).

This shows the possible dangers of applying the doctrine of judicial notice to situations which depend on variable circumstances. The English courts have wisely refused to apply judicial notice to diagnostic use of the X-ray. In *Sabapathi v Huntley*, 1 W W R 817 (1938), on appeal from the Supreme Court of Ceylon the Judicial Committee of the Privy Council held that whether medical standards require X-ray examination in a suspected fracture case calls for expert testimony since the question depends on varied circumstances such as condition of the patient, character of the injuries and accessibility of apparatus. (Accord *Boyce et ux v Brown*, 51 Ariz 416, 77 P (2d) 455 (1938).)

¹¹⁴ For detailed analyses of the American legislation, and other valuable tabulations, see Landman, *Human Sterilization*, N Y (1932), Appendices, p 287.

¹¹⁵ *Myerson, *Certain Medical and Legal Phases of Eugenic Sterilization*, ABA INT Med, 1943, XLIII, 580, 53 Yale L J (April 1943) —

into account in arriving at an enlightened social policy toward dissemination of birth control advice ¹¹⁶

Private Law Doctrine and Medical Practice It is a delusion to speak of "Medical Jurisprudence" in referring to the legal problems which arise from the practice of medicine First, it is customary to reserve the term "Jurisprudence" to connote philosophic ends of law and the main analytical approaches to law as a science In the second place, law is a roof which shelters us all, and those doctrines which touch the doctor belong to large fields of law As a rule, they do not express a unique series of principles applicable only to medical men Liability in damages to a patient allegedly injured by malpractice is governed by the law of Torts ¹¹⁷, whether or not such conduct was so extreme as to be also a crime is tested by principles of Criminal Law Rights of compensation of the physician are determined by the law of Contracts, including doctrines of Quasi-Contract ¹¹⁸ The position of the expert witness is determined by the law of Evidence What may seem to the doctor to be a separate and distinct body of principles is really an integral part of a systematized field of law It is surprising how many of the major fields of law contain doctrines which touch upon the doctor's daily life Medico-legal grounds of annulment or divorce may be pertinent to the proper relief of a patient ¹¹⁹, the law of Wills must determine the validity and effect of the last will and testament signed by a patient in extremis and witnessed by the physician ¹²⁰ The Statute of Limitations may

¹¹⁶ *Rock, Medical and Biologic Aspects of Contraception Scientific Contra-indications to Legal Restriction of Contraceptive Advice, Clinics, 1943, II, 1598

¹¹⁷ Smith, H W, Legal Responsibility for Medical Malpractice, (1941) Jr Am Med Assoc, 1941, (March 8, May 10, May 31, June 14, June 21, July 5) *Scott, Tort Liability of Hospitals, ANN INT MED, 1943, xviii, 630, 17 Tenn L Rev (April 1943) —, *Smith, Legal Liability for Non-Therapeutic Surgery, Ann Surg, 1943, —, —, 14 Rocky Mt L Rev 233

See, also, re law of damages *Ludlam, Plaintiff's Duty to Minimize Defendant's Liability by Surgery, 17 Tenn L Rev (April 1943) —

As to legal aspects of agreements not to compete, see *Dodd, Contracts Not to Practice Medicine, ANN INT MED, 1943, xviii, 618, 23 B U L Rev (April 1943) —

¹¹⁸ Quasi-contract Benefit Voluntarily Conferred Due to Mistake of Material Fact Surgical Services Rendered Gratuitously Under Mistaken Belief That Patient Needed Charity

X, a man of advanced years, did not appear to be an opulent citizen. He was admitted to the out-patient department of a New York City hospital with little or no questioning as to his financial worth He was there diagnosed as suffering from prostatic obstruction and treated as a charity patient for six months His condition then required admission as an in-patient for a perineal prostatectomy It was assumed that since he was an out-patient he was unable to pay for the operation and he promised to pay only hospital charges for his room and board Staff surgeons Y and Z performed the operation gratuitously, assuming that X was a charity case, and X received the operation thinking it would be free One month later X died and it was discovered that he was worth over four hundred thousand dollars Thereupon, Y and Z filed claims against the estate for surgical fees (It is a well settled rule of law that if one makes a gift he is ordinarily debarred from charging compensation for the benefit conferred) Held Y and Z could recover the reasonable value of their services under doctrines of "quasi-contract" They performed the operation gratuitously on the assumption that X was "necessitous" whereas in fact, through a mutual mistake, X was not qualified to receive treatment "gratis" as a charity patient Matter of Agnew (Surrogate Ct N Y), 132 N Y Misc 466 (1928)

¹¹⁹ *McCurdy, Insanity as a Ground for Annulment or Divorce in English and American Law, Am Jr Psychiat, 1943, xc, —, 29 Va L Rev (April 1943) —

¹²⁰ Some interesting English decisions are discussed in Kitchin, Legal Problems in Medical Practice, London (1936), Sec 7, The Patient Makes His Will

forever bar an action brought by or against a physician, if the suit be filed too long a time after the cause of action accrued. Tax laws touch the doctor with the same inexorable impact and authority as other classes of society.¹²¹

It would be too much to ask any doctor to explore the full content, focal and peripheral, of these large fields of law. To guide him, it would seem desirable that this pertinent law be served up to the medical student and doctor on a functional basis, making the daily routine of the physician primary, and pointing out the secondary legal consequences which may attach to given conduct. Such materials could be presented in conjunction with successive subjects of the medical school curriculum, somewhat as shown in the accompanying table.

How may law students be trained to cope with scientific testimony? It is a vain and unnecessary goal to impart a medical or scientific education to the aspiring young trial lawyer. There are, however, fundamental ideas underlying every species of Scientific Proof and these can be conveyed in an interesting and successful manner, in terms of proper approaches to direct and cross-examination. To know the vital premises, and the points where errors are most apt to creep in, to know how to go about weaving the net of proof or exposing its weak strands, to know who are the experts to whom he may resort and what type of aid he may gain from them, these are facts which the graduate of the American law school does not possess. Furthermore, as I think most members of the bar will agree, this training is not easily acquired in the course of trial practice. Such materials could be presented as part of a law school course dedicated to "Trial Practice and Problems of Proof-Making," a fit companion subject for the modern course in Evidence. Proof-making should be regarded as the functional counterpart of the law of Evidence. It should deal with all types of proof in an applied fashion, but with constant regard to controlling principles of substantive law, Procedural Law, the law of Trial Practice, and of Evidence. Such materials might also be brought in by way of illustrating such subjects as Torts, Insurance Law, Damages and Evidence.

Public Law Problems in Medical Practice The problem of medical care comes into swift contact with public law and constitutional law doctrine.¹²²

Most people are familiar with the scientific conquest of syphilis: how Schaudinn discovered in 1905 that it is caused by a spirochaete, the *Treponema pallidum*, how Ehrlich in 1910 contributed to the arsenal of chemotherapy his highly potent remedy salvarsan (arsphenamine), how in 1913 Noguchi demonstrated the constant presence of the treponema in brains of paretics, and how the Wassermann and other blood tests have much simplified diagnosis and enabled early therapy, control and cure. Considering what we now know about this destructive malady, is it not a reproach to social conscience that syphilis is still a rampant disease in these United States?

¹²¹ *Griswold, *The Doctor's Federal Taxes*, ANN INT MED, 1943, LVIII, 647, 32 CALIF L REV (April 1943) —

¹²² *Powell, *Compulsory Vaccination and Sterilization, Constitutional Aspects*, ANN INT MED, 1943, LVIII, 637, 21 N C L REV (April 1943) —

**SCHEME FOR PRESENTING LEGAL PROBLEMS OF MEDICAL PRACTICE IN CONJUNCTION
WITH SPECIFIC SUBJECTS OF THE MEDICAL CURRICULUM**

1 Anatomy

- 1) Legal use to establish identity
 - a) Criminal law to identify body of murdered person in establishing "corpus delicti"
 - b) Civil law to identify persons entitled to property or insurance
- 2) As subject of cross-examination in trying to discredit expert witness

2 Physiology

- 1) Legal aspects of "deception tests" and other physiological procedures

3 Bacteriology

- 1) Legal aspects of blood group determinations and forensic immunology

4 Pharmacology

- 1) Narcotic laws chief requirements and criminal liability for infraction
- 2) Malpractice civil responsibility for negligent use of drugs

5 Pathology

- 1) Rights in dead bodies legal responsibility for wrongful autopsy
- 2) Right to dispose of one's body by contract or will
- 3) Liabilities of clinical pathologists who supervise production of biological materials
- 4) Coroner's office and Medical Examiner system as devices for investigating cause of "sudden death"

6 Physical Diagnosis

- 1) Malpractice legal responsibility for negligent diagnosis
- 2) Compromise settlements and releases mistaken (non-negligent) diagnosis as basis for setting such settlements aside

7 Surgery and Anesthesiology Malpractice

- 1) Legal aspects of preoperative procedures
- 2) Legal aspects of operative procedures
- 3) Legal aspects of postoperative procedures
- 4) Special problems in treating fractures

8 Medicine

- 1) Malpractice problems in the practice of internal medicine
- 2) Legal aspects of "false imprisonment"
- 3) Legal aspects of "libel and slander"
- 4) Business problems in medical practice
 - a) Rights of compensation of the physician
 - b) Sale of a business practice
 - c) Legal aspects of various types of business organizations
 - d) Antitrust laws
 - e) Tax problems
- 5) Main doctrines of Workmen's Compensation insurance, of Life, Health, and Accident insurance, of the law of Damages, and of the law of Evidence, which the doctor as expert witness should know

9 Roentgen-ray, Electro-cardiograph, Electro-encephalograph, Lie Detector, etc

- 1) Malpractice special problems arising from dangerous properties of roentgen-ray and radium
- 2) Evidentiary uses in legal proceedings

10 Preventive Medicine, Public Health, Public Law and Social Problems

- 1) Main constitutional law principles in relation to "Food, Health and Drink"
- 2) Law relating to public health authorities and practice of preventive medicine
- 3) Legal aspects of medical care, legal problems involved in "Medical Economics"
- 4) Premarital examinations
- 5) Medico-legal grounds of annulment and divorce

11 Medical Specialties

- 1) Special legal problems, as for example
 - a) Obstetrics (birth control advice and practice, therapeutic and non-therapeutic abortion, voluntary and compulsory sterilization)
 - b) Forensic psychiatry

Laws providing for compulsory physical examination once a year of the main systems of every man, woman and child will not shock the populace so much as this continued inefficiency. The Supreme Court which upheld

compulsory vaccination¹²³ and compulsory eugenical sterilization¹²⁴ could be expected to uphold such legislation as an intelligent exercise of state police power necessary to protect that most valuable community asset, the public health. Diagnostic centers might be erected at suitable places throughout the land, under proper legislation, to enable the general practitioner to gain those advantages in identifying obscure diseases which are now confined to hospitals or clinics because of the cost considerations.

Such advances will not injure the position of the doctor, but will increase the volume of medical care, raise the level of scientific medicine by closing the gap between general practice and clinical practice,¹²⁵ and bring substantial benefits to each citizen, partially at public expense. No one disputes the desirability of extending horizons of medical practice, and medical men are not so reactionary toward new risk-sharing ideas as some laymen might suppose. These innovations must come in a sound and orderly course, but all can see the current of the times and none can hold it back. Workmen's Compensation Laws, once regarded as a breath-taking social innovation, are now under heavy attack because the allowances for incapacity are too low.¹²⁶ The whole problem of economic security, so far as the wage earner goes, may prove to be inextricably bound up with adequate health insurance.¹²⁷ Increasing the breadth and range of medical care does not require "socialized" medicine or undesirable disturbances of the control or pattern of medical practice.¹²⁸

¹²³ *Jacobson v Commonwealth of Massachusetts*, 197 U S 11, 25 Sup Ct 358 (1905)

¹²⁴ *Buck v Bell*, 274 U S 200, 47 Sup Ct 584 (1929)

¹²⁵ Many communities and doctors are confronted with this problem. Dr Warren F Draper comments on how many young physicians become discouraged by lack of a satisfactory solution and leave private practice for the public health service to regain contact with the full play of scientific methods. Draper, Report of the President (Oct 1942), 17 Harv Medical Alumni Bull 4. The general practitioner cannot afford many of the new instrumentalities for diagnosis and treatment, and frequently this circumstance will force him to surrender the patient to better equipped hospitals.

¹²⁶ Wilson and Levy, *Workmen's Compensation* (1941), Volume II, The Need for Reform.

¹²⁷ Recognition of this fact is one conclusion of the recently completed study of Sir William Beveridge on social insurance and allied services, a 300 page report published by H. M. Stationery Office on Dec 1, 1942. This study, undertaken at the request of Arthur Greenwood, then Minister Without Portfolio in charge of post-war reconstruction, is concerned largely with means for attaining freedom from want. It bids fair to establish new patterns of thought in England regarding needs for more adequate health and workmen's compensation insurance. For American edition of this report, see Beveridge, *Social Insurance and Allied Services*, N Y 1942, Macmillan Company.

¹²⁸ Every individual has a legitimate interest in the betterment of medical services, but all plans should take into account certain ideals and convictions widely held to be of fundamental importance, these being:

(1) There should be no restraint on the opportunity of the medical practitioner to advance according to his merit and special ability.

(2) There should be no such regimentation of medical practice as will remove individual incentive, cause all methods to become stereotyped or interfere with full expression of experimentation.

(3) Control of medical practice and safeguarding of standards should be reposed in the medical profession and not be made a subject of bureaucratic administration.

(4) The economic position of the doctor should be protected in respect to the services which he performs. In the final and fully expanded program of medical care certain to emerge, society should underwrite adequate medical service without having the more unfortunate patient compelled to rely upon charity.

Cooperation of Law and Medicine History is full of cases where doctors or lawyers have mingled their traditions in some fascinating and useful way ^{120, 180, 181, 182, 183}

I like to think upon the affinities of the lawyer, the doctor and all those who probe the sciences. All are bred in the tradition of strict skepticism, all have a respect for the best evidence available to prove an issue, and all must leave the cloistered shelter of their researches to perform the practical tasks of life. By virtue of their strict training and their habitual realism, they are fit to be illuminators of social good as well as prime movers.

These three together, the lawyer, the doctor, and the man of science, can reduce the discordant noise now produced when the striking iron of science meets the anvil of the law. The blacksmith shop may yet become a modern assembly plant, and all three may find themselves companion toilers on a more intricate pattern called "social synthesis."

(5) The extension of medical care, particularly in regard to preventive medicine, might well be implemented by enlightened legislation, consonant with public opinion, arranging for the routine examination of the entire populace at periodic intervals, with provisions for hospitalizing and treating those suffering from contagious disease. At this stage of social evolution, it might be better left to individual choice whether a person suffering from non-contagious disease, constituting no menace to his fellow citizens, should receive curative treatment. In any event we must not confuse this wholesome social planning with either autocratic regimentation or with socialized medicine, for the essential premise simply goes back to the adequate protection of the body social by intelligent use of the means at hand.

¹²⁰ As joint authors they have produced treatises on law-medicine problems. The first of these, *Medical Jurisprudence*, by J. A. Paris, M.D., Fellow of the Royal College of Surgeons, and J. S. M. Fonblanque, Barrister at Law, was published in London, in three volumes, in 1823.

¹³⁰ John Hunter, 1728-1793, failed to maintain his great reputation when giving evidence for the defense in the trial of Donellan (1781) for the poisoning of Sir Theodosius Boughton with cherry laurel water. That one of his medical attainments was able to render such little assistance in the administration of justice, made a deep impression. It may have prompted the efforts of Andrew Duncan which caused a chair of medical jurisprudence to be founded in Edinburgh University in 1807, the first in the British dominion.

¹³¹ In contrast, Sir James Paget (1814-1899), the rare Scotch surgeon who described Paget's disease, made a profound impression as an expert witness in the early and important malpractice case of *Perionowsky v Freeman* (Court of Queen's Bench, 4 Foster and Finlason 977 (1886)). He explained the division of labor between nurse and visiting surgeon in an illuminating way, and the court did not hesitate to declare it as law that a hospital nurse, alone, is responsible for negligence in carrying out merely ministerial duties, such as giving the patient a bath. Unless the negligence goes on in his presence without objection, the surgeon cannot be held for her carelessness in having the water too hot and thereby scalding the patient.

I might mention, too, Ambrose Pare, the father of French surgery, who published in 1575 his work on monsters, simulated diseases, and a method for preparing medical reports.

¹³² Clark Bell, born in Jefferson County, N. Y., in 1832, became an eminent lawyer. He was counsel for promoters of the Union Pacific Railway Company, and as such prepared the enabling acts passed by Congress, under which the road was constructed. He was deeply interested in law-medicine cooperations, served for several years as President of the Medico-Legal Society of New York, established its library, founded the "Medico-Legal Journal" in 1883, and in 1885 represented North America at the conference in Antwerp convened to develop an international classification of mental diseases.

¹³³ Marshall Hall was a colorful English barrister of the past generation. Son of a doctor, he was named for Marshall Hall, the great English physician of the nineteenth century. As a young man Marshall Hall made himself an authority on materia medica, and he put this knowledge to repeated use in his trial work. His special talents led him to be engaged as counsel in a series of celebrated causes, including the trial of Frederick Henry Sedgwick at the Old Bailey in 1912 for alleged poisoning by arsenic. He was deeply interested in all species of Scientific Proof and made a prize collection of fire arms and lethal weapons. See Marjoribanks, *The Life of Sir Edward Marshall Hall* (1929).

CLINICAL APPROACH TO ALLEGED TRAUMATIC DISEASE *

By LEOPOLD BRAHDY, M D , and SAMUEL KAHN, M D ,
New York, N Y

EVERY part of the body is daily subject to all kinds of minor traumata, of which the individual is usually only vaguely conscious. When, following any such trauma, undue symptoms appear, the patient promptly recalls the recent injury and tends to attribute to it the condition from which he suffers. If the accident was an unusually dramatic one, a patient will be even more convinced that his condition resulted therefrom, even though it occurred long before the symptoms became manifest.

In eliciting the history in such a case, it is important to remember that the patient's opinion as to the relationship between an injury and a subsequently developing disease is often sincere. Many women give a history of having struck the breast only a day or two before they became aware of the presence of a breast tumor. With no conscious or subconscious motives to influence them, they are convinced that that trauma is the cause of their condition. To the examining physician, whose knowledge is based on the biology of tumor growth, it is obvious that the tumor mass must have been of palpable size for weeks before the contusion and that it must have existed, though smaller, for many months. The physician should assume that his patient's opinion and history are sincere unless there is unquestionable evidence of conscious malingerer. By such an attitude the physician may be able to induce the patient to recall hitherto untold facts, which may furnish a sounder basis for an opinion on causal relationship and which may even change the patient's own conviction.

The patient's conviction rests on the principle of *post hoc propter hoc*. All of us are heirs to this ancient fallacy. In guarding against it, the physician may easily fall into another error, i e., refusal to accept a cause and effect relationship, because he cannot visualize the steps in pathogenesis whereby the results of the injury become manifest as the disease. He may become so exacting in his demand for scientific standards of evidence that he often completely ignores clinical experience. And yet, the question of causal relationship between trauma and disease is largely a clinical problem. It is part of the clinical study of the etiology of disease.

In this, as in any other medical problem, the physician eagerly seeks the help of the pathologist, the laboratory worker and the statistical analyst, but he must depend primarily on accurate and detailed clinical observation. Records of court verdicts in other similar cases should not influence his opinion. The conclusions of a lay jury and of a learned judge can have

* Received for publication February 8, 1943

little value in the determination of the etiology of disease. The physician must rely solely on medical data and on prevalent medical authority. If litigation is involved, he must completely ignore the effect his opinion may have on the patient, the lawyers and the tribunal. Whether a plaintiff, defendant, or a Court seeks his advice, conclusions reached by the physician must be based solely on the facts and must be identical in content and emphasis.

When a physician who does not specialize in traumatic medicine or surgery is called upon to treat an injured person, he is interested only in the immediate medical problem, and pays no attention to a possible medical or legal sequel. How the accident occurred, and where, and why, and which parts were injured aside from those requiring treatment are questions of little importance to him. But long afterwards, when a lawyer is consulted, in a suit for damages or compensation, the details concerning the accident and the injury may become paramount. Especially is this true if the patient later has a disease which may or may not have resulted from the injury sustained.

With relatively few exceptions, there is no one exclusive cause of disease. Several factors, in varying combinations, act as synergists, and produce the conditions under which a disease develops. Of these factors, one may be a constant, like the bacteria in infectious diseases. But this constant factor alone will not necessarily produce its disease. The tissues of the body must permit the invading bacteria to grow and multiply. If the body is too resistant, the bacteria will die, and the disease will not develop. If, however, there is insufficient body resistance or if the bacteria light on some devitalized tissue, they will there find a favorable site for growth, and disease will appear. This inconstant, secondary factor of resistance is, therefore, as important as the specific bacteria.

Malnutrition is often a non-specific, secondary factor whose effects are better known than those of trauma. A review of the rôle of malnutrition may suggest the proper approach to the study of trauma.

Malnutrition is the direct cause of certain diseases—scurvy, neuritis, rickets. It is a secondary factor in producing other conditions, for example, pulmonary tuberculosis, although many cases of tuberculosis develop without it and although most undernourished people do not develop tuberculosis. Malnutrition, therefore, is not a constant factor in the etiology of tuberculosis but is a recognized one in some cases. The malnutrition may, on the other hand, be the result of the disease, rather than one of its causes. Malnutrition may also co-exist with tuberculosis without affecting it or resulting from it. No generalization on causal relationship should be applied in the case of an individual who is tuberculous, each case must be studied separately.

Like trauma, malnutrition is a primary or secondary cause of many conditions, but there are some in which it plays no part. Hodgkin's disease occurs in the hungry as well as in those who are well nourished. Though little is known of the cause of Hodgkin's disease, in any specific case no

physician would hesitate to assert that malnutrition did not cause or activate or accelerate it

Again, like trauma, malnutrition is of varying degrees and of various types. Deficiency of one vitamin may be the cause of a specific disease which could not be caused by a general reduction in diet. The disease must be accurately diagnosed, as well as the type of malnutrition afflicting the patient, before any conclusion as to the causal relationship between them can be reached.

As a factor in the causation of disease, trauma should be studied in the same way as malnutrition. The literature on the relationship of trauma and disease has increased in the last decades, but much still remains obscure. Certain diseases in which trauma was believed to play a part are now known to be entirely unrelated to it. Other conditions, it is now known, may be caused by trauma: a skin burn can produce a duodenal ulcer, a back injury, with negative roentgen-rays six days after the accident, may be the cause of a compression of the body of a vertebra found six months later.

The rôle of trauma, like that of malnutrition, is analogous to that of any other inconstant, nonspecific factor in the causation of disease. An injury may be the direct cause of a disease, as in the case of septicemia resulting from a puncture wound, it may precipitate the symptoms in a previously asymptomatic condition, such as tabes or general paresis, it may accelerate an existing disease, for example, pulmonary tuberculosis, it may only temporarily aggravate a chronic process, such as diabetes mellitus, it may result in serious, acute damage because of the presence of an underlying chronic condition, as the production of gangrene by moderate trauma in the presence of obliterating thromboangitis, it may direct the attention of the patient and physician to a preexisting disease which was unaffected by the trauma, as when examination of the breast, following a mild contusion, reveals the presence of a neoplasm. Finally, the possibility of a disease causing an accident, instead of a trauma influencing a disease must be considered, for example, a spontaneous pneumothorax, due to the rupture of an emphysematous bleb, can cause the operator of a car to lose control of it, with resulting serious injury to himself.

According to their relationship to trauma, diseases may be divided into three classes

- 1 Those which are practically always the result of injury. When a patient sustains a contusion, a laceration or a fracture, the physician can express an opinion on causal relationship without undue deliberation, since such conditions belong to the group which are almost always traumatic in origin. Since the relationship of these diseases to trauma is clear, they will not be considered further in this discussion.

- 2 Those which are never the result of trauma. In some diseases, such as measles, this is obvious. In others, as for example, colloid goiter, the problem is more complicated. The clinical evidence of the rôle of trauma

must be evaluated, statistical analyses of series of cases, experimental laboratory reports, and the pathology of the disease must all be given due weight. If it is decided that trauma never plays any part in the development of a disease, then it belongs to this second group. Obviously, in any specific case of such a disease, the question of causal relation to trauma must be answered in the negative.

3 There remains a group of diseases which usually develop spontaneously, but in which trauma may be a causative factor, such as myocardial infarction, duodenal ulcer, and abscess of the kidney. In this group of diseases the question of causal relationship must be considered separately in each individual case.

We shall indicate the facts which may have a bearing on the relationship of an injury to a subsequently appearing disease, and outline the principles upon which the reasoning is based. The facts to be considered are the following:

- 1 The diagnosis of the disease
- 2 The physical and mental condition of the patient prior to the injury
- 3 The injury, its type, its site, and its severity
- 4 The immediate objective and subjective effects of the injury
- 5 The intercalary period—also called the latent period or the time interval
- 6 The bridging symptoms
- 7 The biology of the disease

Accurate Diagnosis Before an opinion on causal relationship can be reached, it is essential to diagnose the condition from which the injured patient is suffering. Diseases due to trauma must be differentiated from those with somewhat similar symptoms which are unaffected by trauma. When a paresis of the injured arm was found in an elderly man who some time before had sustained a simple Colles' fracture, it was necessary to determine whether the paresis was the residual of an old hemiplegia or a hysterical manifestation. If it was a hysterical manifestation, the injury may have been its cause. When symptoms suggestive of Parkinson's syndrome are found after an injury to the head, it must be borne in mind that true paralysis agitans is not traumatic in origin, but that a severe injury of the basal ganglia may produce signs and symptoms similar to those of true paralysis agitans. Accurate diagnosis is obviously fundamental in deciding on causal relationship in such a case.

Frequently, reëxamination of the patient at intervals may reveal data helpful in establishing a diagnosis, and, equally important, in determining the stage of development of the disease and its post-traumatic course. If, following a fracture of the ribs, tuberculosis of the lung is found, and the lesion runs an unfavorable course thereafter, the question of traumatic activation of a quiescent condition must be carefully considered, but if the lesion progresses toward healing, it may be concluded that the fracture caused neither aggravation nor activation of the preëxisting tuberculosis.

The Condition of the Patient Prior to the Injury Because periodic routine medical examinations are infrequently made, a precise knowledge of an individual's pretraumatic status is usually lacking. The increasing trend toward preemployment and periodic examinations may make available, in the future, many important data concerning the status of individuals prior to their injuries. Records of previous medical examinations will throw light on many obscure cases, but they can also be misused. When men are examined superficially because of lack of time required for careful study, it is improper to use such examination records to prove the absence of some obscure ailment, whose discovery depends upon meticulous investigation.

When data concerning the patient's condition before the injury are not available, an attempt must be made to estimate that condition on the basis of the clinical history, the findings immediately after the injury, and the patient's past activities. Where litigation is pending, too much reliance should not be placed on an uncorroborated history, since some patients may conceal a preëxisting condition in the hope of benefiting their claims. A man who did satisfactory work, which required much strength and exertion, was clearly not suffering from cardiac insufficiency. Should symptoms of decompensation develop soon after a severe chest injury, a causal relationship between the two is probable. A claim that epileptiform seizures resulted from an injury must obviously be considered fraudulent, if the co-workers of the patient had seen him in similar attacks before the injury. If a lung cavity is found by roentgenogram or clinical examination immediately following an accident, it is evident that pulmonary tuberculosis preëxisted.

There are many difficulties in estimating the pretraumatic condition of an injured person. As the statements of the patient and his friends cannot be wholly relied on, the conclusions reached concerning the prior status of the patient can only rarely be definite.

The Injury—Its Type, Site and Severity Having determined, as far as possible, the status of the patient before the accident, the physician should consider how the injury occurred—the physics of the injury—exactly what happened. Experience and patience are required to induce a person to describe the exact site of the injury, and to obtain the data necessary for a determination of the severity of a blow. If the injury was caused by a falling object, an effort should be made to discover its size and weight and the distance through which it fell. If the injury resulted from a strain, the size and weight of the object lifted, as well as the position of the patient, may furnish a clue to the severity of the strain. The necessity for determining the severity of an injury need not be stressed. The late effects of a severe blow or strain are as different from those of a light one as are the immediate effects.

Traumata are of several kinds: direct (blows or falls), indirect (sprains or twists), and psychoemotional. In certain diseases, for example, duodenal ulcer, a direct blow may be a determining etiological factor, whereas an

indirect trauma is not. In others, the converse is true. The effects of psychoemotional traumata are often far reaching, even though associated with little physical injury. Toxic thyroidism is the most dramatic example of organic disease resulting from psychic trauma.

A disease which is caused by an injury usually will manifest itself at the site of the injury. It is essential, therefore, to discover just where the force of a blow was exerted, or where its force may have been projected.

The greater the distance of the disease from the site of the injury, the less is the likelihood of any causal relationship. A blow in the lumbar region may result in tuberculosis of the kidney, a blow to the head may precipitate the symptoms of general paresis, but a blow on the thigh can have no direct effect on either condition.

There are exceptions to this general principle that a pathologic process resulting from an injury manifests itself at the site of the injury. When a thrombus is liberated because of a trauma, the embolic effects of the thrombus will appear far from the site of the trauma. When the skull or chest is injured, the effect of the injury may be projected to a point opposite the site of injury—the point of contrecoup.

The Immediate Effects of the Injury In considering whether a disease has been caused, precipitated or accelerated by a trauma, the signs and symptoms which appeared immediately after the trauma should be carefully scrutinized, and the extent of the immediately resulting disability determined. The patient should be permitted to narrate the circumstances of the accident and its immediate consequences before specific questions are asked. In his digressive and often irrelevant rambling, he may describe important events which might have been omitted in the course of the examiner's formal inquiry. Allowances must be made for the tendency on the part of the injured person to exaggerate his symptom and to overemphasize his physical defects, especially when litigation is pending. Some individuals exaggerate and dramatize their symptoms in every illness. The patient with a claim for damages should not be expected to recite his history and enumerate his symptoms more accurately than does a patient who suffers from a non-traumatic condition. The physician must sift the history and subjective symptoms, rejecting what appears to be false, accepting what seems reasonable and discounting tactfully and patiently what is exaggerated.

In getting a history from a patient about the immediate effects of an injury, it is well to avoid leading questions. "Were you unconscious after you fell?" will elicit the answer "Yes," if there is intentional exaggeration. However, "What did you do after you fell?" may elicit from the same person the answer "I felt to see if my head was bleeding" or "I shouted for help." The last two answers indicate that there was no unconsciousness, a fact which may have an important bearing on the question of causal relationship.

Whenever it is possible to discover them physical signs are more reliable criteria of the immediate effects of an injury than are the patient's

history and complaints A hematoma, or a disturbance in reflexes, or an abnormality of a joint is more significant than is a complaint of weakness or of pain in the extremity

Whenever there are witnesses to an accident, lawyers or investigators inquire minutely into the events preceding the accident and into the accident itself This evidence is important, of course, for legal, and even for some medical purposes Too often, however, investigators neglect to obtain a description of the patient's actions and appearance immediately after the injury Such information is of great medical value If this information were more carefully sought and submitted to the physician, medical opinion on causal relationship would be more easily reached and more accurate and valuable These immediately post-traumatic signs and symptoms constitute the best gauge by which to determine the severity of the injury The extent of disability following an accident is an indicator of the intensity of the resulting pain and of the presence of dysfunction of one or more of the vital organs A claim that a strain resulted in an attack of angina pectoris may be considered, if the patient suffered such immediate severe pain that he was disabled If he continued at his work, the claim is not plausible Traumatic epilepsy can be caused by brain injury severe enough to have produced unconsciousness If the injured person was neither unconscious nor disabled after the accident, it can be concluded that the injury probably bears no relationship to a later appearing epileptic attack

The Intercalary Period The time interval (latent period, intercalary period) between the occurrence of a trauma and the appearance of symptoms and signs of the resultant disease is analogous to the incubation period of infectious diseases In infectious diseases a certain time elapses between the invasion of the body by the infecting organism and the clinical manifestation of the disease This time, within known limits, is specific for each infectious disease During this time the organisms grow and spread and finally produce their disease Similarly, in traumatic disease, a time interval is necessary for the development of the pathologic process initiated by the trauma This interval, like the incubation period in infectious diseases, varies with the disease which the trauma has produced The upper and lower limits of this developmental period are not definitely established in many pathologic conditions, and consequently, wide leeway must be allowed in specific cases

In some conditions the time interval is always short, as in angina pectoris following a strain In others, it is long, as in traumatic epilepsy In still others the intermediate period may vary from a few hours to a few months or longer, as in septicemia Since this disease is an extension of a local infection, it can occur long after the appearance of the local traumatic infection, and even long after the local condition has been apparently healed

When an abscess is found an hour after an injury, or when a renal calculus is found after a few days, there can be no causal relationship between the injury and these conditions The time interval is too short

Both the abscess and the kidney stone require a longer time to develop. A preexisting kidney stone, however, may be dislodged by a trauma, which precipitates the symptoms of renal colic. If that occurs, the symptoms of the colic must appear almost immediately after the trauma. Should they appear after the lapse of a few days, they cannot be attributed to the trauma, the time interval is too long.

In many conditions, such as tuberculosis of the kidney, traumatic epilepsy, ureteral stricture, the trauma initiates a pathological process which is relatively asymptomatic, and which produces symptoms of the usually non-traumatic disease only after a long intercalary period.

Bridging Symptoms The injury, its immediate effects, and the time interval having been considered, attention must be given to the symptoms which manifest themselves in the interval between the time of the injury and the first appearance of the resultant disease. It is important to know the time of appearance of each symptom and of its recession, but it is frequently difficult to fix the patient's attention on this temporal sequence. An injured person often remembers the date of the first appearance of those symptoms which persist, but he is usually inaccurate about those symptoms which came and went.

After the acute symptoms directly due to the trauma have subsided, and before the patient is ill with the ensuing disease, intermediate symptoms may appear. They are known as bridging symptoms. These symptoms serve as signposts to the physician that some condition is developing, the nature of which has not yet become clinically manifest. The presence or absence of these interval symptoms often is the determining factor in the final decision on the probable relationship of injury and disease. It must, of course, be definitely established that none of the slowly emerging signs and symptoms was present prior to the injury. In some diseases, for example pulmonary tuberculosis, the diagnosis of tuberculosis may not have been made until many months after the injury occurred, but careful questioning of the patient may show that mild symptoms were present during this long interval or, possibly, even before the accident. In some diseases, if there is a continuity of symptoms and signs from the time of the injury to the clinical appearance of the disease, there may be causal relationship between the two, in other diseases, the reverse is true. For example, syphilis may appear at the site of an earlier fracture of a bone. Causal relationship is plausible, if the condition was not physiologically cured for a long time following the fracture, as evidenced by persistent circulatory disturbance at its site, with resultant swelling and pain, which became more intense until syphilitic bone changes appeared. In tuberculosis of bone, on the contrary, if caused by an injury, there is usually a free interval after the signs of injury have disappeared and before the symptoms of the bone tuberculosis are manifest.

The Biology of the Disease The pathologic process which is the basis of the disease precedes its first signs and symptoms. On the basis of these first clinical manifestations, the physician must estimate the date at which

this pathologic process was initiated. In order to conclude that the intercalary period is consistent with causal relationship between trauma and disease, or that it is too long or too short to be consistent with causal relationship, the physician must know the early stages of the biology of the disease.

An opinion on whether the trauma accelerated or precipitated the disease requires a picture of the course of the disease in the traumatized patient, both before and after the trauma occurred. In order to judge whether there is a change due to trauma, the physician must know the usual non-traumatic mode of onset of the disease, its usual course, the ordinary variations from this course, the average frequency of recurrences and exacerbations, and the end results when that disease is uninfluenced by secondary factors such as trauma. Only with this knowledge can he judge the possible effect of trauma. If, after injury, tuberculosis of the lungs is stationary, or if it progresses slowly toward healing, it is reasonable to conclude that the trauma had no aggravating effect on the disease. The appearance of minor symptoms after trauma or slight increase in symptoms is ignored (from our standpoint) because tuberculosis normally shows minor variations in symptoms even under the best conditions. It is, therefore, not reasonable to ascribe such changes to a secondary factor—trauma. If a previously asymptomatic pulmonary tuberculosis spreads rapidly after an injury, however, there is ground for considering the question of the trauma accelerating the previously quiescent pathological process. The fact that a disease process becomes worse following a trauma is not in itself sufficient evidence that the trauma accelerated the disease. Cancer of the stomach will grow and metastasize without any intercurrent injury, just as it will following injury.

Rarely are all the medical data complete, and, even then, there are uncertain factors which enter into the determination of the causal relationship between trauma and disease. In view of the diversity of well considered opinion in some diseases, in view of the difficulty of obtaining even from honest patients a precise history of their condition before and after trauma, in view of the fact that some patients may exaggerate or lie in order to support their claims for damages, no one should express an opinion on the relationship between a trauma and an ensuing disease without careful study of the specific case. A more extensive literature of carefully studied clinical and pathological material will be a potent aid to physicians, perhaps enabling them one day to speak categorically on causal relationship. At present, the evidence and knowledge obtainable usually permit a physician to conclude only that a trauma probably did or probably did not produce, precipitate or accelerate a disease. Nevertheless, a physician should not hesitate to state his conclusion after study of all the factors we have discussed. It is not necessary to equivocate, even though our knowledge of the secondary factors in the etiology of disease, such as trauma, does not yet constitute an exact science.

PROBLEMS OF PROOF IN CLAIMS FOR RECOVERY FOR DERMATITIS *

By LOUIS SCHWARTZ,† *Bethesda, Maryland*

WORKMEN'S compensation laws are designed for the purpose of reimbursing the worker for loss of earnings and cost of medical care resulting from occupational injuries or occupational diseases. This immediately brings up the question of a definition of an occupational disease.

Many definitions have been given and, as is the case with most definitions, objections can be made to all of them. Among those suggested are the following:

1 An occupational disease is one which occurs as a result of exposure to a recognized specific occupational hazard. It must have the accepted physical signs and symptoms of the specific disease caused by exposure to the specific occupational hazard.

This definition leaves no room for inclusion of newly discovered occupational diseases, nor for old ones with unusual or newly discovered symptoms and physical signs.

2 Occupational diseases are abnormal bodily or mental states directly resulting from exposure to harmful substances or conditions directly related to work (McCord).

This is a broader definition, but still leaves open the question of "harmful substances or conditions."

3 Occupational diseases are the outcome of long exposure to noxious influences during work occurring with particular frequency among workers in a specific industry.

This definition would leave out occupational diseases caused by short exposures to noxious influences, such as dermatitis¹ caused by primary irritants, cyanosis² which may be caused by short exposure to aniline,³ or caisson disease⁴ which may be caused by rapid decompression. Such diseases would have to be classed as occupational accidents, because of their sudden onsets. Compensation should be given for disease caused by the occupational environment rather than for diseases coming within the terms

* Received for publication February 2, 1943.

From the Division of Industrial Hygiene, Dermatoses Investigations Section, National Institute of Health.

† Medical Director, U. S. Public Health Service.

¹ Dermatitis—inflammation of the skin.

² Cyanosis—a bluish discoloration of the skin, particularly noticeable in the nail beds and lips, due to inadequate oxygenation of the blood.

³ Aniline—an organic compound widely used as the starting point for the synthesis of such substances as dyes, medicinals, etc.

⁴ Caisson's disease—a condition affecting individuals who are too rapidly subjected to decreased atmospheric pressure, such as deep sea divers coming to the surface or airplane pilots ascending too rapidly.

of the above definitions For instance, if it can be proved that a worker contracted typhoid fever⁵ from drinking polluted water at his place of employment and nowhere else he should be entitled to compensation, regardless of the fact that typhoid fever is not classed as an occupational disease, and regardless of whether his employer was or was not at fault in supplying such water

State compensation laws^{1, 2} are not uniform but can be grouped into three classes

1 The schedule method in which only certain specially named diseases are compensated, with a description of the process in which the disease must occur in order to be compensable (Del , Mich , Minn , N J , N Y , N C , Ohio , Pa , R I , Wash , Ky , Mass , Neb , W Va)

2 The general or blanket coverage method in which any and all occupational diseases are compensated, without defining the term occupational disease (Calif Mo , N D , Wis)

3 The general coverage method, with a statutory definition of the term "occupational disease" (Conn , Ill , Ind)

Although occupational dermatitis is mentioned specifically in only a few of the State compensation laws, nevertheless it can be included in most of the above classes and even in the compensation laws of those States in which only occupational accidents are compensated This is so because the hearings before compensation boards are informal, the laws are broadly interpreted, and the worker always gets the benefit of the doubt Moreover, compensation commissions are not only referees, but investigators Since dermatological investigation is necessary to diagnose and determine the cause of dermatological conditions, all compensation commissions should have available at least one impartial dermatologist⁶ who is specially versed in occupational skin diseases The duty of such a dermatologist would be to inform the commission in regard to the following (1) Do the working conditions present an actual occupational dermatitis hazard? (2) Has the worker an occupational dermatitis? (3) What is the actual cause of it? (4) Was it contracted at the place against which the claim is made? (5) Is or was the employee disabled by it? (6) Give an estimate of the time of disability (7) Express an opinion as to measures to be employed to prevent the recurrence of the condition (New occupation, protective apparatus or clothes if worker returns to same occupation)

All dermatoses which affect workers are not necessarily of occupational origin, therefore, a worker claiming compensation for an allegedly occupational dermatitis must prove its occupational origin Here we must differentiate between a dermatitis directly caused by the worker's occupation

⁵ Typhoid fever—a specific bacterial disease frequently acquired from drinking water that has been contaminated with excreta from a person harboring the causative organism

⁶ Dermatologist—a physician specializing in diseases of the skin

and one which is caused not by the occupation but by the occupational environment. For instance, if a worker is exposed to a skin irritant in the course of his work and as a result contracts a dermatitis on the exposed parts, that dermatitis is directly occupational, but if the worker contracts a dermatitis of his buttocks, because he is sensitive to the paint or wood of the toilet seat³ which he uses at his place of work the dermatitis is caused by his occupational environment and not by his occupation.

It is desirable to learn whether an occupational dermatitis is caused by a substance which will cause dermatitis on any one under similar working conditions, or whether it is caused by a substance which will affect only certain workers who are sensitized to it. In the first case, the substance is designated a *primary skin irritant*, in the second, a *sensitizer*. A *primary cutaneous irritant* is an agent which will cause dermatitis by direct action on the normal skin at the site of contact if it is permitted to act in sufficient intensity or quantity for a sufficient length of time. A *cutaneous sensitizer* is an agent which does not necessarily cause demonstrable cutaneous changes on first contact but may effect such changes in the skin that, after five to seven days or more, further contact on the same or other parts of the body will cause dermatitis.⁴

The physician not versed in occupational processes and occupational skin hazards does not usually go to any great lengths in examining the occupational hazard or history of the patient before making a diagnosis of occupational dermatitis. This is especially so in states where the compensation laws do not require adequate diagnostic criteria and are so worded that if a physician undertakes to treat a worker and makes a diagnosis of occupational dermatitis his fee is guaranteed by the compensation commission or the insurance carrier. But if he makes a diagnosis of non-occupational dermatitis, he must look to the patient for his fee. This encourages diagnoses of occupational dermatitis.

There is no one factor on which a diagnosis of occupational dermatitis can be made. All of the following factors must be considered and properly evaluated.

1 History This must show that such a dermatitis was not present before the patient entered on his present occupation. It must show that the dermatitis developed during a period of occupational exposure or after a lapse of a reasonable incubation period following the cessation of exposure. This period should not be under a week. If the physician knows that other workers similarly employed are similarly affected, then the diagnosis of occupational dermatitis is more likely to be correct than if his patient is the only one of a group who is affected.

If the patient has previously had similar attacks when working with the same chemicals, the chances that he has an occupational dermatitis are increased. If the history shows that dermatitis occurs whenever the worker is at work, improves or disappears when he is away from work for a few

days, and recurs soon after he returns to work, then there is established a definite cause and effect relationship between the occupation and the dermatitis

2 Site of the Eruption The site of the eruption is important, because occupational dermatitis begins on the parts most exposed to the irritant the fingers, hands, and forearms if the substance is handled, the face and neck where the industrial operation gives rise to dust, vapors, and fumes, and the covered parts of the body when the irritant penetrates the clothing Especially is this so if work clothes and underclothes are not changed daily and if shower baths are not taken before leaving the work place Portions of the body subject to friction are often sites of occupational dermatitis; the wrist, the belt line, the ankle at the shoe top, the neck at the collar line—all are sites where irritants may be rubbed into the skin Sometimes an irritant not strong enough to cause dermatitis on the fingers, may be carried by the hands to the tender skin under the eyes and cause dermatitis there Sometimes an occupational dermatitis may become generalized Especially does this occur in workers who have a high degree of sensitivity and who are entirely exposed to irritant penetrating dusts, fumes, or vapors, or who work for long periods without changing work clothes

3 Appearance of Lesions This is not characteristic except in a few classes of occupational irritants Paronychia⁷ and onycholysis⁸ are common occupational lesions among fruit and vegetable canners, dish washers, soda fountain attendants, scrub-women, and housewives Acne-like lesions,⁹ folliculitis,¹⁰ and boils on the arms and legs are characteristic occupational lesions among workers exposed to cutting oils, crude petroleum, heavy coal tar distillates, and certain viscous and wax-like chlorinated hydrocarbons Hydrosopic chemicals, such as sugar, salt, and lime and the volatile solvents, will in time cause the skin to become defatted and fissured

4 Differential Diagnosis The common non-occupational diseases of the skin, such as seborrheic dermatitis,¹¹ pityriasis rosea,¹² erythema multiforme,¹³ neurodermatitis,¹⁴ fungus infections¹⁵ and their allergic manifesta-

⁷ Paronychia—infection, usually with a pus producing organism, around the edge of a nail

⁸ Onycholysis—partial separation of a nail from its nail bed

⁹ Acne—an inflammatory disease of the sebaceous (oil) glands of the skin, especially common on the face, back, and chest and characterized by black heads, and "pimples"

¹⁰ Folliculitis—inflammation of the structure around a hair root

¹¹ Seborrheic dermatitis—a skin disease, subacute or chronic, affecting usually the scalp, area around the nose, and middle of the chest and back, and characterized by greasy scales

¹² Pityriasis rosea—a self limited skin disease affecting the skin of the trunk especially, and the extremities to a less extent, characterized by oval, reddish, scaly "spots" that vary from $\frac{1}{4}$ to $\frac{3}{4}$ inch in diameter

¹³ Erythema multiforme—a skin disease with a number of causes and characterized by various types of lesions varying from reddish to purple "spots" to blisters and occurring especially on the extremities

¹⁴ Neurodermatitis—a chronic skin disease of unknown origin characterized by itching redness, and thickening with exaggeration of the normal furrows of the skin

¹⁵ Fungus infections—a skin infection with a pathogenic fungus, a well known example being "athlete's foot"

tions,¹⁶ and contact dermatitis¹⁷ caused by irritants encountered outside of the work shop, must be differentiated from occupational dermatitis. It is true that the presence of these diseases does not exclude the presence of an occupational dermatitis. In fact, an occupational dermatitis may more easily occur on a skin which is already damaged by another skin disease.

The fungus infections and their allergic manifestations, the so-called phytids, cause the most controversies before compensation boards. The defendants often contend that the skin disease for which the worker claims compensation is not occupational, but is of fungus origin. Especially is this the defense when the worker is found to have a definite fungus infection of the feet, groin, or other parts of the body not exposed to the occupational irritant. In these cases the defendant claims that the skin lesions on the exposed parts are also fungus infections or the result of allergic manifestations to the fungus infections (dermatophytids). The various tests with trichophytin¹⁸ are of little value in making a differential diagnosis because they are nearly always positive as most persons have had these infections. They are of value only in the rare cases in which the tests are negative because then they tend to show that the claimant has had no fungus infection. But even if it is shown that the claimant has an active fungus infection or phytid, this does not rule out the possibility that he may also have an occupational dermatitis. In fact, it is held by some authorities that an allergy to fungus infections predisposes to allergic occupational dermatitis. I cannot subscribe to this theory. Although I agree that a skin damaged by the lesions of a fungus infection is more easily irritated by an external irritant than the normal skin, and may even grant that such a damaged skin may be more easily entered and sensitized by a sensitizing substance, I cannot conceive that sensitivity to a specific substance predisposes to sensitivity to an entirely different substance. If this were so, our accepted theories of specific sensitivities and specific immunities on which rests much of our therapy would have to be entirely revised. Those of us who are allergic to some substance, and many of us are, would all tend to become allergic to many substances, and those of us immunized to one disease, such as typhoid or smallpox, would tend to become immune to all diseases. The facts are exactly the opposite. Most of us do not take on new allergies, but tend to lose the ones we have. Children affected with the so-called atopic eczemas¹⁹ tend to lose them as they grow older. Grown ups sensitive to ragweed do not as a rule become sensitive to other plants. Those immunized against

¹⁶ Allergic manifestations of fungus infections (dermatophytid)—a dermatitis usually occurring on the hands, and especially the palms, characterized by deep-seated blisters, redness, and occasionally itching. It is an allergic manifestation of a focus of fungus infection at another site, i.e. the feet, groin, etc.

¹⁷ Contact dermatitis—a dermatitis resulting from an irritant substance coming in contact with the skin.

¹⁸ Trichophytin—an extract of a certain pathogenic fungus or fungi used for doing skin tests the results of which are useful in determining whether the individual is or has been infected with certain fungi.

¹⁹ Atopic eczemas—dermatitis characterized by redness, and tiny blisters, and usually itching. It is caused by a substance acting from within the body, such as a certain food.

smallpox must also be immunized separately against typhoid, yellow fever, typhus fever, plague, or whatever other disease they are to be protected against

It is also difficult to differentiate occupational from non-occupational contact dermatitis. The lesions and sites are similar and only a careful elicitation and consideration of all the facts can lead to a correct understanding of the cause. In these cases and in differentiating fungus infections, the patch test is of great value.

The patch test is based on the theory that if a dermatitis is caused by hypersensitivity to a certain substance, such substance when applied to an area of unaffected skin of the susceptible individual and left on for a period of time will cause an inflammation at the spot where it touches the skin. In doing patch tests, it is important to know what concentrations of certain chemicals can come in contact with the normal skin for a stated period of time without causing an inflammation or reaction. It is also important that no primary irritants, such as strong acids or alkalis, be used in the patch test, as they will burn any skin. The portion of the body on which a patch test is to be performed is also of importance because it has been found that the different portions may vary in sensitivity to certain chemicals. For instance, the tough horny skin on the hand is less susceptible to irritants than the more tender skin on the inner surface of the forearm. For this reason, patch tests performed on uninflamed skin adjacent to the eruption are more likely to give reactions of diagnostic significance than when performed on more distant areas.

If the worker is handling known irritants and his fellow workers are also affected, the cause is obvious and the patch test is unnecessary, but if he is the only one of the group who is affected, then he should be tested with the materials with which he comes in contact in the course of his occupation. If he is patch tested with only one substance, a control patch should be also used. If the subject is tested with more than one substance any negative reaction from one of these substances serves as a control.²⁰ It is also desirable to use as a control one of the workers who has no dermatitis.

In patching with solids, best results are obtained by moistening them, preferably with perspiration obtained from the armpit of the patient. Sometimes it may be necessary, in order to obtain a reaction from a patch test, to use perspirations of differing hydrogen ion concentrations. The results of patch tests must be correlated with the worker's particular occupation, the history of the dermatitis, and the site and morphology of the lesion, in order to arrive at a correct etiologic diagnosis.

Patch tests are only a link in the chain of evidence on which a diagnosis of industrial dermatitis is made. A positive reaction shows only that the portion of the skin on which the patch was applied was at that time sensitive.

²⁰ Control—a test which is identical in all respects to an experimental test except for the omission of the substance which is being tested, or using the identical test on another person who is then the "control."

to the particular substance. In order to state that this substance was the cause of the occupational dermatitis, we must be sure that the patient was exposed to the substance in the course of his work and presuppose that the patient's skin was also sensitive at the time of industrial exposure.

When negative results are obtained from patch tests with the materials met with in the course of the patient's occupation, we must not conclude too hastily that the dermatitis is not of industrial origin, for one or more of the following reasons:

- 1 The skin area over which the patch was placed may not be hypersensitive, whereas the area covered by the eruption may be hypersensitive.

- 2 If the eruption has disappeared the patient may no longer be sensitive when the patch test is performed but may have been sensitive at the time he had the eruption and when he was industrially exposed.

- 3 A negative reaction may be due to the fact that the patch test never accurately reproduces actual working conditions, such as friction, maceration, heat, cold, and sunlight, which may be additional factors adding to the irritating effect of the substance to which the patient is exposed.

- 4 It may be that the concentration and amount of the chemicals applied as a patch test may not be as great as they actually were during industrial exposure.

- 5 Finally, the actual industrial irritant may not have been discovered and applied as a patch test.

When negative reactions are obtained from patch tests with substances encountered in the work room and the dermatitis which the worker has resembles a contact dermatitis, an effort must be made to perform patch tests with materials met with in the patient's home, which may be the cause of dermatitis. Certain plants, or perhaps paints, or even new furniture are examples of such materials. Tests of this kind will in some cases show that the patient is sensitive to materials met with outside of industry, and is not sensitive to the materials with which he comes in contact in his place of employment.

The technic of performing patch tests is important. When testing for hypersensitivity to primary irritants, such dilutions must be used in the tests as are known not to irritate the normal skin.⁵

The ordinary procedure in performing a patch test is as follows. A sample of the material to be tested is first placed on a suitable skin site—the inner surface of the arm or forearm, or the back usually being chosen. If the material to be tested is a solid it may be used as such, or a piece of gauze about four ply thick and a quarter to a half inch square may be moistened with water or perspiration and impregnated with the material. In the case of liquids or solutions of the substance to be tested, the gauze square is dipped in the fluid and applied to the skin. Again it is emphasized that only

those materials, or proper dilutions of substances in solution, should be used that are known not to affect the normal skin. Over the patch test substance, or the gauze patch impregnated with this substance, is placed a piece of insulating material about an inch square, and a two inch square of adhesive is placed over all to hold the patch in place. The insulating material inserted between the chemical and the adhesive plaster should be a non-irritant substance, such as unvarnished cellulose or, better still, a thin sheet of mica may be used. The resin on waterproof cellophane itself may be an irritant as may be some of the compounds in dental rubber. The adhesive plaster used to hold the patch in place often causes an erythema²¹ of the skin. The patch test is allowed to remain on the skin for 24 to 48 hours before removal and the site is observed for several days thereafter for determination of the result.

Patch tests are considered negative (—) when no reaction occurs at the site in contact with the substance being tested. A transient erythema that does not persist at least twenty-four hours is also considered negative. Positive patch tests are usually graded from one plus (1 +) to four plus (4 +) depending on the severity of the reaction.

At the time the patches are removed there may be no reaction present, but some time later, a few hours to a few days, a delayed reaction may develop at the site of the patch. We should regard delayed reactions as denoting a lesser degree of hypersensitivity than undelayed reactions provided the concentration and amount of the patch testing substance is the same and the area covered by the patch is the same.

Patch tests properly performed and evaluated can be of great help in the diagnosis of industrial dermatitis, but if improperly performed and evaluated, they may lead to confusing and unjust conclusions.

Allergy as a Cause of Occupational Dermatitis Allergy is a word to denote an altered reactivity in human beings or in animals caused by a first contact with a substance and manifested after an interval of time (period of incubation) upon second contact with the original or identical substance. A standard medical dictionary, however, defines it as "A condition of unusual or exaggerated specific susceptibility to a substance which is harmless in similar amounts for the majority of members of the same species"⁶. This definition differs radically from the first by the fact that it does not presuppose that sensitization is caused by the first contact and that it develops only after a period of incubation has elapsed, and only after another contact has occurred.

The "allergy" as defined by the dictionary may be caused by a visible or demonstrable breach in the defense mechanism of the skin, such as abrasions, disease of the skin, thinning of the epithelium, loss of the normal fluids of the skin, etc., which enable an irritant to enter it easily. But the conception of the first definition implies that changes, caused by the first contact,

²¹ Erythema—redness of the skin due to congestion of blood in the skin capillaries

so condition the skin, even though no change is demonstrable, that after a period of incubation has elapsed, second contact with the substance causes a dermatitis. If the first definition is to be accepted, then allergy causes less than 20 per cent of all occupational dermatitis.⁷

Allergy should not be a bar to compensation for occupational dermatitis. Allergic occupational dermatitis usually develops in new workers about five days to three weeks after beginning work. In most cases, if the worker is able to keep on working, the dermatitis clears up—the worker becomes “hardened.” Only a small percentage of such cases do not develop this “hardening.” The worker should be removed from the job if the dermatitis does not clear up after two months of treatment or if he develops recurrent attacks of dermatitis while working.

A chronic dermatitis more or less generalized occasionally occurs in a worker, usually passed middle age, the cause of which it is almost impossible to determine. Such a worker's history shows that he has worked at the same occupation for many years without any trouble and then suddenly develops a dermatitis which persists even though he stops working for a long time. An examination of his work may reveal no new chemicals or changes in process to which the dermatitis can be attributed. The claim is made that the worker has become sensitized to some substance or substances in his work and that as a result of that sensitization he has become sensitized to many other substances which are not connected with his work. Therefore, he cannot get well even though he leaves his job. There are many dermatologists and allergists who will support such a contention. But they cannot prove that the patient did not first develop a sensitivity to a substance met outside the working environment, and that the occupational sensitivity did not follow and was not secondary to the non-occupational one.

Patch tests on such persons are unsatisfactory and sometimes impractical because the patient may be feeble and the risk of a flare-up of the skin lesions cannot be taken, or there may be no normal areas of skin on which a patch test could be performed. Such a damaged skin may react to anything in the form of a patch test. If such patch tests are performed and results are positive, it may be concluded that his occupation is at least a contributing factor to the dermatitis. Even if the patch test shows negative reactions to the substances in his working environment and positive reactions to non-occupational ones, it still can be argued that this is only presumptive and not positive proof that he was not sensitive to those substances in his occupational environment at the time that he first became sensitized. This would imply that the worker originally developed a dermatitis as a result of becoming sensitized to some substance encountered in his occupation. Following this he developed a polysensitivity—that is, he also became hypersensitive to substances encountered elsewhere than in his occupational environment. Subsequently, and prior to the time of patch testing, he lost his original hypersensitivity to substances encountered at his occupation but retained his

hypersensitivity to the substances encountered away from his occupational environment. This contention should not be supported. If it is, then every allergic condition in a worker which first manifests itself after he begins to work can be reasoned to be of occupational origin. Besides, such a theory is contrary to the accepted theories of specific sensitivities and specific immunities. In fact, it is usual for new workers handling sensitizing chemicals to develop an allergic dermatitis five days to three weeks after beginning work, and for the large majority of them to get well, become "hardened" as the workers call it, and work without further trouble, they become desensitized instead of polysensitive.

But even if we should admit that one sensitivity predisposes to another and finally to polysensitivity, it would still remain debatable whether polysensitivity causing a chronic persistent allergic dermatitis in a worker is the result of an occupational sensitivity first acquired to which the non-occupational sensitivities are secondary, or vice versa.

Polyvalent sensitivities causing allergic generalized eczemas also occur among people exposed non-occupationally to sensitizers. Their causes are many and often undetermined. It is true that if such a worker shows a positive reaction to a patch test with any of the substances which he encounters in the course of his work, his occupation should be considered to be at least a contributory cause of his dermatitis, but if the patch tests with these substances are negative, or are not performed, then the occupational etiology of his dermatitis has not been established and is open to question.

Claims have been made before compensation commissions that the ordinary skin diseases of unknown etiology, such as psoriasis²² and lichen planus,²³ are caused by the worker's occupation. The physician on the witness stand is often asked, "Well, Doctor, since the causes of this disease are not known, is it not possible that the plaintiff's occupation was the cause of it?" Answer yes or no. The physician should answer "No," and then explain that if the plaintiff's occupation were one of the causes of the disease, then a large percentage of the workers employed at it would also be affected, which of course is not so.

It is possible that new lesions of psoriasis and lichen planus may appear on areas of skin which have been injured in the course of work, as is the case in injury from any cause, but the psoriatic tendency was present before the trauma. So, although new lesions which occur on areas of the skin occupationally traumatized may be said to be occupational, this cannot be said of the disease entity itself.

Occupational Cancer It is generally recognized that tar, soot, pitch, crude petroleum, the actinic solar rays, roentgen-rays, and radium have car-

²² Psoriasis—a common skin disease of unknown cause characterized by scaly erythematous plaques found most frequently on the knees, elbows, and on the scalp.

²³ Lichen planus—a skin disease of unknown origin occurring frequently on the extremities, characterized by elevated, flat-topped angular papules. There is usually some itching.

cinogenic properties Workers with these substances who develop carcinoma²⁴ can claim that it was caused by occupational exposure, but it must be remembered that the normal incidence of cancer among human beings must also be taken into account Occupational skin cancers have certain characteristics

They always appear on parts exposed to the carcinogenic agent

They are often multiple and recurrent

They are always preceded by a precancerous lesion

They always appear in workers who have long been exposed to the carcinogen

They usually do not have metastases²⁵

For instance, if a worker develops a cancer on the face and it is shown that in his occupation he is exposed to the fumes of coal tar pitch, it is likely that the cancer is an occupational one But if a similar worker develops a cancer of the lower lip and it is shown that he is a pipe smoker, the occupational origin of his tumor is, to say the least, questionable

Workers exposed to alpha- and betanaphthylamine and benzidine in synthetic-dye plants who develop tumors of the bladder have a legitimate claim for the occupational origin of the tumors Workers in radium mining who develop carcinoma of the lungs can also rightly claim occupational origin Physicians and laboratory technicians who work with roentgen-ray or radium and develop carcinomata of the hands have a legitimate claim of occupational cancer Radium can also cause cancer of the bones, especially if it is ingested But the actinic-ray cancers on the exposed parts of workers in sunny tropical climes are not so clearly of occupational origin, because they live in that climate and are still exposed to the actinic rays when they are not at work

The rôle of arsenic as a cause of occupational cancer is open to debate There is no doubt that the long-continued oral ingestion of inorganic arsenic can cause palmar and plantar keratoses²⁶ But to claim that the cancer appearing on the face or hands of a farmer is due to the arsenical insecticides which he may use is rather far fetched, especially when the farmer is also exposed to actinic rays Examination, by the author, of many hundreds of workers with arsenical insecticides and other arsenic compounds has failed to show any skin cancers The medical records of the factories in which these persons were employed also failed to show skin cancers Reports of State compensation boards received by the author for the past 10 years fail to show any skin cancers attributed to arsenic, although there are many reported as caused by coal tar and petroleum

²⁴ Carcinoma—a cancer, or malignant growth

²⁵ Metastases—a malignant growth occurring in another part of the body from that of the original malignancy, having reached its new site through the transportation of cells from the original growth by lymph and/or blood vessels

²⁶ Keratoses—a horny growth on the skin

The reports of cases of occupational arsenical cancers by certain authors are open to the criticism that the etiology of the cancers was not proved but inferred. The proof usually consisted of the fact that the worker said he handled arsenic, or he was a miner of ore which may have contained arsenic. "Post hoc, ergo propter hoc." This is poor evidence.

Trauma as a Cause of Cancer. Cancer when it occurs is often attributed to faintly-remembered blows. However, blows are of common occurrence, whereas cancer at the site of trauma is extremely rare. Therefore, the burden of proof of trauma causing cancer is on the claimant. He must first show that the part was normal before the trauma; that the blow was a severe one, or very often repeated, and included the site of the tumor, that a sufficient interval elapsed between the occurrence of the injury and the appearance of the tumor, that a biopsy²⁷ verifies the carcinomatous nature of the tumor.

Chronic occupational irritation may be a cause of cancer.

Cancers arising in scars resulting from occupational injuries can certainly be called occupational.^a

The Physician and the Compensation Commission. Every physician making a diagnosis of occupational dermatitis should fill out the following questionnaire in reporting his case.

SKIN CLINIC

DATE

NAME

AGE

RACE

TYPE OF SKIN (DRY, MOIST) (THICK, THIN, PARCHMENT-LIKE) (DARK, LIGHT, FRECKLED)

CHAPPED

PREVIOUS SKIN DISEASES

HISTORY OF ALLERGY (hay fever, asthma, plant poisoning, etc.)

NAME OF EMPLOYER

MANUFACTURE WHAT

BRIEFLY DESCRIBE WORK

PRESENT WORK BEGAN

PRESENT DISEASE BEGAN

CHEMICALS OR SUBSTANCES CONTACTED

DESCRIBE LESIONS

²⁷ Biopsy—examination of a piece of tissue, including microscopic examination removed from a living subject for purposes of diagnosis.

PATCH TESTS PERFORMED

SUBSTANCES	CONCENTRATIONS	TIME	REACTIONS
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
DERMATITIS CAUSED BY.	.		.
..
DIAGNOSIS BASED ON	.		.
.....	.		.
..
TREATMENT GIVEN
..
PREVENTIVES ADVISED	.		.
..
ADVISED CEASE WORK..	How LONG		.
REMARKS	.		.
.	.		.
.	.		.
.	.		.
.	.		.

The answers to these questions will enable the commission to judge the criteria on which the diagnosis is made

If the physician is to appear before the commission he should make himself thoroughly familiar with the occupational process at which the patient works, the health hazards involved, the occupational history of the patient, and the literature concerning the hazards of the patient's occupation. He should be familiar with all the diagnostic tests involved and should be prepared for a rigid cross examination.

The expert physician should confer with the lawyer before the trial and coach him as to what questions to ask on direct examination to best bring out the evidence in favor of his client. He should also instruct the lawyer on weak points in the case of the opposition so that he can cross examine to the best advantage the expert physician on the other side of the case.

The physician on the witness stand should answer the question as put (if his counsel does not object), but if an explanation is necessary, he may give it after answering the question. He should never hesitate to say "I don't know" when he does not know. It makes what he does say much stronger, and may keep him out of trouble.

For instance, a certain well known dermatologist testifying before the Federal Trade Commission in the case of a progressive lead hair dye which was advertised as stimulating the natural pigment-forming cells of the scalp

testified that the preparation was a dye. He was asked on cross examination "Would it dye cotton?" After hesitating he answered "Yes." Whereupon the lawyer placed some cotton in the colorless liquid hair dye, allowed it to stay in for a while, then pulled it out to show that it was not dyed. The physician was chagrined, and the incident tended to belittle the physician's qualifications as an expert. He should have answered, "I do not know. I never tried to dye cotton with it." Fortunately the author was present and knew that lead salts could be made to dye cotton if the cotton was first treated with a sulphur compound so that it contained sulphur, as does the hair. He asked the lawyer (for the Government) to put him on the stand and ask the same question, to which the same answer was given, and a piece of white gauze was first dipped into a solution of sodium thiosulphate, allowed to dry, then immersed in the colorless lead hair dye solution. After a few minutes, when lead sulphide was formed on the gauze, it was seen to turn dark.

The physician should also confer with counsel so that he may know how to bring out facts showing that the medical qualifications, experience, ethics and standing of an unscrupulous expert are not of the best.

Dermatitis from Wearing Apparel and Cosmetics Dermatitis allegedly caused by wearing apparel, cosmetics, and jewelry is frequently reported, but when we consider that the entire population is constantly exposed to them, we realize that the percentage of the population affected is almost negligible.

The records of the casualty insurance carriers for 1941⁹ show that only 78 claims for dermatitis from wearing apparel and cosmetics were reported to them. The table below classifies these cases according to cause.

Wearing Apparel		Cosmetics	
Hat bands	12	Hair preparations	16
Pajamas	9	Soaps	6
Underwear, women's	6	Face creams	6
Hose, women's	5	Nail polish	2
Dresses, women's	3	Mascara	1
Shorts, men's	3	Face powder	1
Wrist watch straps	3	Deodorant	1
Clothes, men's	2	Hand lotion	1
Dress shields	1		
Total	44	Total	34

The National Retail Dry Goods Association sent a questionnaire to its members asking the number of claims they had for dermatitis from January 1, 1940 to July 1, 1941⁹. Fifty stores reported that they had no complaints, 60 stores reported 656 cases, classified as follows:

Wearing apparel, women	425
Wearing apparel, men	61
Cosmetics	61
Miscellaneous	9
Not accounted for	100
Total	656

One hundred and thirty-three stores reported that they had complaints, but did not give the number of them, nor the year in which they were made. They were classified as follows

Number of stores reporting complaints from wearing apparel and cosmetics—

From dresses	14	From cotton	5
From rayon	13	From pajamas	5
From furs	11	From jewelry	4
From corsets	10	From underwear, women's	3
From hosiery	10	From garters	3
From wool	9	From miscellaneous	21
From underwear, men's	8	From cosmetics	10
From coats	7		
		Total	133

The stores reporting to the National Retail Drygoods Association reported only 17 of these cases to the insurance carriers so that there is but little duplication in all of these figures. Therefore, it is safe to say that there are less than 1,000 cases of dermatitis per year allegedly caused by wearing apparel and cosmetics among 130 million people. This is one case per 130,000 and even less, for when we examine the reports we find that only a small percentage of the claims were proved, if judged by accepted medical criteria.

Only a few of these cases went to trial. Most of them were either dropped or were settled by crediting the merchandise, by paying the medical bills, by small cash settlements, or by combinations of these.

Allergenic substances are the principal causes of dermatitis from wearing apparel, and there will always be some people who are allergic to substances which are harmless to by far the large majority.

Hair wave preparations, hair dyes, medicated soaps, skin creams, and nail polish are the principal cosmetics reported as causes of dermatitis. The hair wave preparations are strongly alkaline and are classed as primary irritants, but the hair dyes, soaps, creams, and nail polish are only sensitizers.

In looking over the claims we note that the products complained of were made by a few manufacturers. For instance, all the hat band complaints were against one large hat manufacturer. The wrist-watch strap complaints were all against one product. The large majority of the hosiery and pajama complaints could be traced to one finish. Most of the hair-preparation complaints were against two or three cosmetic trade names, and all the nail-polish complaints were against one maker of nail polish. Therefore, it must be presumed that the manufacturers used some unusual or new chemicals in their products, or that they were careless in their manufacturing processes. Furthermore, it must be presumed that they did not perform approved toxicity tests on the products before selling them to the public.

It seems likely that if the plaintiffs in these cases had known that many others were being affected by the same products, they could have made a strong case against the manufacturers.

Except for the occasional outbreaks of dermatitis from new and untested products, the majority of the claims for dermatitis from wearing apparel and

cosmetics are either due to the constitutional idiosyncrasy of the plaintiff, or they are false

It is not difficult to determine the cause of a dermatitis due to wearing apparel or cosmetics. Such an eruption begins at the site of contact with the irritant, usually five days or more after the first contact, provided there is at least a second contact at the lapse of this period, or if the contact has been continuous or intermittent. This is the period of incubation for the establishment of sensitivity. The eruption may occur sooner if the article of wear or the cosmetic contains a primary skin irritant, or if the patient has previously been sensitive to the sensitizer in the garment or the cosmetic.

The eruption is usually confined to the sites touched by the irritant. Only in exceptional cases is there a generalized eruption. The eruption disappears or improves when the offending garment or the cosmetic is not used, and becomes worse or returns every time it is again used.

It is possible to find the actual chemical in the garment or cosmetic which is the cause of the dermatitis. Methods for determining this have been devised^{9, 10}. It may be a long and difficult process in an individual case, and not of sufficient importance to warrant spending the time, but every physician making a diagnosis of dermatitis from a fabric or cosmetic in the case of a patient who intends to claim damages should be at least required to fill out the following form. If he does this properly, he will make a favorable impression on the witness stand and escape much embarrassment on cross examination.

- 1 When did patient buy the garment or cosmetic?
- 2 From what firm?
- 3 Date when it was first worn or used
- 4 Date when eruption was first noticed
- 5 What parts of body were first affected?
- 6 Give order in which eruption spread
- 7 Describe entire extent of eruption
- 8 What previous skin diseases did the patient have?
- 9 Has the patient a history of skin or mucous membrane allergy?
- 10 What drugs, if any, does the patient use?
- 11 What laxatives?
- 12 What sedatives?
- 13 Were any drugs taken before present eruption?
- 14 Was poison ivy or other irritant plant contacted before eruption?
- 15 Is the eruption still present?
- 16 When was use of garment or cosmetic discontinued?
- 17 How long after this did the eruption persist?
- 18 Were patch tests performed?
- 19 If so, with what substances. Describe tests in detail and give results
- 20 If no patch tests were done, give reasons for not doing them
- 21 Has the actual chemical causing the dermatitis been found?

- 22 Describe how this was accomplished
- 23 Summarize the facts on which you base your diagnosis
- 24 What treatment was given?
- 25 Give prognosis

Before testifying in court the expert must make himself thoroughly familiar with all the aspects of the case and with the medical literature pertaining to such cases. The counsel and the expert dermatologist, before appearing in court on claim cases, should discuss the merits of the case so that they can agree on the questions which, on direct examination, will best bring out the facts to prove their claims and to refute the claims of their opponents.

Some Points the Plaintiff Should Try to Show The plaintiff should try to show—

- 1 That there were many other users similarly affected
- 2 That the material causing the dermatitis was made with chemicals which are notorious sensitizers
- 3 That the materials causing the dermatitis contained new chemicals or chemicals not previously used in such materials
- 4 That the manufacturer did not properly ascertain the skin irritating properties of the product before offering it for sale
- 5 That the particular garment was not properly processed according to the accepted custom of the trade, i.e., "dirty fun", finish not properly applied, dyed, etc.
- 6 Patch tests properly performed on patient and controls show that garment or cosmetic is a primary irritant or sensitizer, and was the cause of the dermatitis
- 7 That the patient was not sensitive before the substance was used
- 8 That using the substance was the cause of the sensitization
- 9 That using the material caused the eruption to appear or get worse, and vice versa
- 10 That the plaintiff was not allergic to any other substance which may have caused the dermatitis

Some Points the Defendant Should Try to Show

- 1 That although there were thousands of users of similar substances, the plaintiff was the only one affected
- 2 That the substance contained no primary irritants nor strong sensitizers
- 3 That the substance contained no new chemicals or chemicals not previously used in such materials
- 4 That the substance was made in the usual manner in which such substances are made and approved by the trade
- 5 That the new chemicals used, if any, were properly tested by recognized authorities and found to be no more irritating than chemicals commonly used for the same purpose

- 6 That the finished product was properly tested by recognized authorities on a sufficient number of people and found to be no more harmful than other similar substances before it was placed on sale
- 7 That the particular garment or cosmetic used by the plaintiff did not differ from all the others which had been sold and which caused no trouble
- 8 That the dermatitis of the claimant did not have a cause and effect relation with using the substance, i e , that it did not begin where the substance touched the skin, that it appeared, disappeared, got worse, improved, regardless of whether the substance was or was not used
- 9 That the patch tests were negative, or if positive, were not properly performed or evaluated, i e , patch tests made with extract of substance, permitted to remain on too long, patch tests were more severe than actual use, no control patches nor control persons were used
- 10 That the disease was not a contact dermatitis, but something else
- 11 That the plaintiff is allergic to other substances which may have caused the dermatitis

BIBLIOGRAPHY

- 1 SAPPINGTON, C O Medicolegal phases of occupational diseases, 1939, Industrial Health Book Company, Chicago
- 2 HUSSEY, RAYMOND Workmen's compensation and medicine, Med Clin N A, 1942, W B Saunders Co, Philadelphia, pp 1035-1051
- 3 TULIPAN, LOUIS Toilet-seat dermatitis, Indust Med, 1940, ix, 303
- 4 Proceedings of the First Meeting of the Consulting Staff of the Dermatoses Investigations Section April 20-21, 1942 (unpublished)
- 5 SCHWARTZ, LOUIS Sensitivity to external irritants in industry, New York State Jr Med, 1936, xxi, 1969-1976
- 6 DORLAND, W A NEWMAN The American illustrated medical dictionary, Eighteenth Edition, 1940, W B Saunders Co, Philadelphia
- 7 SCHWARTZ, LOUIS Allergic occupational dermatitis, Jr Allergy, 1940, xi, 318
- 8 SCHWARTZ, LOUIS, and TULIPAN, LOUIS A text book of occupational diseases of the skin, 1939, Lea and Febiger, Philadelphia
- 9 Personal communication from National Retail Drygoods Association
- 10 SCHWARTZ, LOUIS, ET AL An outbreak of dermatitis from resin fabric finishes, Jr Am Med Assoc, 1940, cxv, 906-994

CIRCULATORY DEFICIENCY IN THE EXTREMITIES IN RELATION TO MEDICO-LEGAL PROBLEMS: ARTERIOSCLEROTIC DEFICIENCY (INCLUDING DIABETES); THROMBOANGIITIS OBLITERANS, OR BUEYER'S DISEASE *

By JOHN HOMANS, M D , *Boston, Massachusetts*

INTRODUCTION

THE diseases to be described are able to reach their full development in the absence of injury, and often do so. As a rule, injury is an aggravating factor, hastening the development of the disorder—precipitating it in some instances—bringing out a latent condition. Occasionally, however, as in the case of thrombosis of a blood vessel, a blow, fall or strain may appear in any one instance to be the sole recognizable cause of the disease. From a medical point of view, the distinction between an aggravation and a basic cause is significant. From the medico-legal standpoint, it is less so. In workmen's compensation cases, for example, the insurer is equally liable, whether a circulatory disorder is aggravated or the individual breaks a bone. As far as possible, in the following account of various circulatory diseases, it will be pointed out how injury may affect them and under what circumstances it is most likely to do so. But medical conceptions are far from fixed and, very often, authoritative pronouncements are not available.

CIRCULATORY DEFICIENCY IN THE EXTREMITIES

ARTERIOSCLEROTIC ARTERIAL DEFICIENCY

The two varieties of chronic circulatory deficiency, due respectively to arteriosclerosis (hardening of the arteries) and thromboangiitis obliterans (Buerger's disease), have much in common. Arteriosclerosis occurs in the elderly as a result of the wear and tear of life. Thromboangiitis obliterans, which is of unknown origin, attacks a far younger group. Both diseases, however, cause a serious deficiency in the supply of arterial blood in the affected limbs. The upper extremities, though actually subject to both diseases, are rarely so changed as to offer a clinical or medico-legal problem. The lower limbs are the ones seriously affected, and the descriptions which follow concern only them. Much of what is said, under the heading of Arteriosclerotic Arterial Deficiency, of the nature of a defective arterial circulation, applies to Buerger's disease as well, for example, the tests for arterial deficiency and the reaction to injury. To avoid repetition, a reasonably complete account of these subjects is given under Arteriosclerotic

* Received for publication January 23, 1943

Arterial Deficiency, and allusion is made to this in the description of thromboangitis obliterans. Thus the account of the two diseases should be read together.

Pathology Both large and medium sized arteries are hardened by arteriosclerosis. Calcium salts are deposited in their walls, making them still more inelastic and causing them to cast a shadow in the roentgenogram. They are narrowed in a patchy manner by the formation of mural thrombi within them. This erratic narrowing, by restricting the arterial supply of blood, leads to ill-nourishment of the tissue which they serve, affecting especially the toes. The ill-nourishment is seldom equally distributed as between two limbs and even as between toes, muscles and skin. It causes shrinkage of the tissues, that is, of the skin, fat, and muscles, tending to make them inelastic and even fibrous. They cease to react in a normal way to injury and infection, but they need exhibit no obvious change in appearance. Such changes as are present are usually irreversible, though their further development is often checked by the establishment of alternate routes for the blood stream, the opening up of a "collateral" circulation on a large or small scale.

When a more complete arterial deficiency is added by a thrombosis* which actually obstructs one or several vessels, then more or less rapidly death of some terminal part of a limb occurs—toes, foot, even lower leg—a change known as necrosis or gangrene. Necrotic parts are especially likely to be the scene of infection which often spreads to nearby tissues. Under favorable circumstances the gangrenous part is gradually isolated, a line of demarcation separates it from the adjacent living tissue and, after weeks or even months, it is finally cast off. Healing may then occur spontaneously.

Symptoms Premonitory symptoms, if any, are coldness and pallor of the feet and lower legs, moderate atrophy (shrinkage) of the soft parts, and a peculiar lameness on walking. Known as "intermittent claudication" or "intermittent limp," this lameness, in the form of a cramp-like pain, sets in regularly when the individual has covered a certain distance at a certain pace. It is relieved in a few minutes by rest but returns upon the same

* The term, thrombosis, applies to a biological process which may occur within both arteries and veins. Certain elements (platelets) of the blood, becoming adherent to the wall of the vessel, are agglutinated into a framework in which the red and white cells and newly formed fibrin become entangled. The resulting firm mass grows by a process of secondary coagulation and, if it plugs the vessel, may spread along it for a considerable distance, becoming softer and more clot-like as it grows. Scientifically speaking thrombosis thus differs from coagulation or clotting, which only occurs within blood vessels after death, or outside the body, or as a process altogether secondary to thrombosis (as just explained). To laymen and indeed to many medical men, thrombosis and clotting mean the same thing.

A thrombus may be "mural," merely narrowing without obstructing a blood vessel, or it may obstruct it for a considerable distance, growing on, as a rule, until it meets the vigorous current of an entering branch, when it is likely to become organized (invaded by fibrous tissue).

The cause of thrombosis is presumably a combination of circumstances among which injury, disease of the vessel wall and slowing of the blood stream are especially important. So far as the arteries are concerned, arteriosclerosis decidedly exposes them to thrombosis (and, as will presently be seen, thromboangitis obliterans does also). Hence the familiar narrowing by mural thrombi and the occasional plugging of arteriosclerotic vessels.

amount of exercise. Evidently it is related to a deficient blood supply of the muscles, perhaps to an unnatural accumulation of waste products.

A more advanced stage is marked by a change toward a deep red or bluish-red color of the toes on dependency, by spontaneous pain in the discolored parts, especially on elevation to the horizontal or higher, and by the appearance of sores or actually gangrenous (necrotic) areas beside the toenails, on the tips of the toes or over a bony prominence such as the great toe-joint. This advance in the disease is usually, though not invariably,

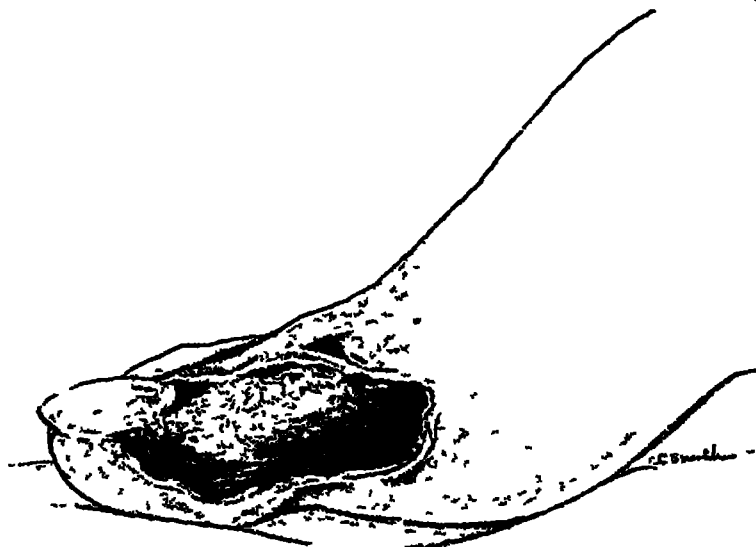


FIG 1 Arteriosclerotic gangrene—dry, mummifying type. The gangrenous area lies on the mesial surface of the right great toe. Such a state might be present in any arteriosclerotic limb, whether or not diabetes was a factor.

irreversible. Unless favorably influenced by treatment, it is the precursor of a serious gangrene.

In diabetics the same events occur, but at a slightly earlier age (since diabetes brings on arteriosclerosis), and, in addition, small joints often become infected and small bones necrotic to a degree that the deficiency in the circulation does not seem to warrant. These infected or necrotic bones or joints, without superficial gangrene, are usually painless. Resistance to infection or injury is even feeble than in uncomplicated arteriosclerosis.

A very advanced stage is marked by gangrene of toes and feet, by infection spreading into joints and upward by way of the lymphatics * (lymph-

* The lymphatics are very fine, delicate vessels which collect the tissue fluid all over the body and empty it into the great vein (vena cava) just before it enters the heart. The lymphatics of each limb pass through a group of lymph nodes, or glands, which act as filters and, by the activity of their abundant cells, free the lymph from bacteria or other noxious material carried in it. Thus, the lymphatics have an important defensive function in freeing the tissues of organisms hostile to the body. But in carrying out the vital function, the lymphatics themselves often become inflamed, a condition betrayed by red streaks visible in the skin and leading from the infected focus in the toes or foot toward the root of the limb. Such inflammation is called lymphangitis and the secondary inflammation of the lymph node is called lymphadenitis. Lymphangitis is always a danger signal, indicating that infection is out of local control in the region where it has started. If the lymph nodes fail to put up a successful defense, bacteria will enter the general circulation.

angitis), by way of the subcutaneous tissues (cellulitis) and along the tendons and muscles. Such states, unless checked by amputation, are often fatal. A very sudden arterial thrombosis, closing a large vessel, may cause a rapid, extensive gangrene with prostration and even death.

The course of arteriosclerotic arterial deficiency is usually slow. In the absence of injury, of infection and of serious exposure to cold, a mild arterial deficiency is compatible with restricted or even relatively normal activity for many years. An individual may be unaware of any disorder, though subject to the bad effects of any of these accidents. He or she would be most apt to notice cold feet, lessened vigor of locomotion (or even intermittent claudication) and pallor with reduced size of the legs.

Diagnosis When invoked as a cause of a circulatory disorder, a diagnosis of arteriosclerosis should be looked upon with doubt, if made upon individuals under 60 years of age, though undoubtedly the disease occasionally occurs at an earlier age, and especially, as already explained, in diabetics. There is no definite clinical picture of arteriosclerosis per se. The hardening and narrowing of the arteries certainly restrict the blood supply of the limbs, which require at moments of active exercise a greatly increased supply of all the materials carried to them in the blood. Even these vessels, however, are usually able to care for the needs of parts not in very active use. Thus, until the disease is serious enough to interfere with the nutrition of resting limbs it need cause no signs. In other words, the disorder caused by arteriosclerosis is at first functional and only in its more advanced stages destructive. The blood stream, restricted in certain areas, is often supplemented, even fully restored, through small vessels opened up under the "stimulus of necessity," a "collateral" circulation.

The tests detailed below are especially helpful in determining the state of the circulation in the lower limbs. By their aid and by the light of the symptoms and physical signs, an authoritative diagnosis should be made.

Tests for Arterial Deficiency To prove that an arterial deficiency exists, it is not enough that the individual should be aged, or even that his palpable arteries, such as those of his wrists and ankles, should feel hard, that is, arteriosclerotic, to the touch.

The Roentgen-Ray If a deficiency is known to exist, the presence of calcification (bony change) in the arteries, as shown in a roentgenogram, is evidence of arteriosclerosis as opposed to any other sort of arterial disease. Calcification in the roentgenogram, however, in the absence of the signs of early or advanced arteriosclerotic disease already described, is not proof of clinical arterial deficiency, though it suggests that such may be present or may readily occur. It suggests, in fact, a latent, not active disease. Moreover, calcification in the vessels of one part is no proof that a similar state will be found in another, though it is of course suggestive. For that reason, courts should require, and counsel seek, roentgenograms of the region of injury involved in the parts under litigation.

Color Changes The normal color of the fingers and toes is some shade of pink, varying from a very pale tint almost to red. The shade is influenced by the state of the surrounding temperature, for the finer vessels of the feet and hands respond to cooling by constriction (causing pallor and conserving heat) and to warming by dilatation (reddening the skin and dissipating heat)



FIG 2 Moderately advanced thromboangitis obliterans. Dark color of the skin indicates deep redness. Black skin indicates gangrene, as of a toe. There is swelling (edema) of the forefoot, as well as of the toes. Such feet would show no pulsating arteries.

At the rather neutral, standard temperature of 70° to 75° F, the extremities should preserve at least a faint pinkness, though the temperature of the skin will become, not that of the body (98.6° F) but nearly that of the air. In these surroundings it will feel objectively, to the examiner's touch, neither hot nor cold. As against this background, the following color changes give sufficient evidence as to the state of the circulation.

- 1 A dead-white, cold extremity is one in which the arterial circulation has, at least for the moment, become so restricted that it may be said to have ceased.
- 2 A blue, cold extremity is one in which the circulation is greatly restricted and probably slowed.
- 3 A red, cold extremity is one, like the preceding, in which the circulation is greatly restricted and slowed, and differs from the blue, cold extremity only in that the blood has not given up its oxygen (thereby failing to make the usual change from arterial to venous blood).
- 4 A red, hot extremity is the seat of inflammation. Even a deficient circulation permits some warming from this cause.

Simple Clinical Tests **Elevation and Depression** The color of the feet at room temperature being known, the legs are elevated by the examiner to an angle of about 30° with the horizon for a period of two minutes. If the toes retain any pinkness, the arterial circulation is at least fair. Retention of most of the normal pinkness means a normal circulation. The state of the two feet may be compared*. While the feet are elevated the shade of pinkness may be studied by compression of the tip of a great toe. The white compression-spot makes a contrast with the surrounding skin and should normally regain its color in several seconds.

On lowering the legs the time required for pink flushing of the feet and toes is normally five to ten seconds. A flushing time of 20 to 30 seconds is very slow, indicating a much restricted and slowed arterial flow. If a slow flushing is followed by a deep red or bluish-red color in the toes while they are allowed to remain dependent, this indicates again a very poor circulation.

The Pulses of the Feet Palpable pulsations in the arteries of the feet are evidence of a good arterial circulation. Various degrees of feeble pulsations in any one vessel are significant. There being two palpable pulsating arteries in each normal foot, i.e., the dorsalis pedis upon the instep, and the posterior tibial below the inner ankle bone, absence or feebleness of one arterial pulse is important unless the pulse in the second vessel is exceptionally strong (anatomic anomaly of no significance). In general, the state of the pulses corresponds remarkably well with the other tests just described.

When color and temperature changes indicate a deficient arterial circulation, it is rare to find any but absent or feeble pulsations in the arteries of the feet in question.

On rare occasions, absence of pulsations will be noted in the presence of reasonably normal color tests. Such a finding indicates that a collateral circulation by way of very fine vessels has replaced the normal flow through the usual large pulsating arteries. This is far more often seen in thrombo-angitis obliterans (see below) than in arteriosclerosis.

THE RELATION BETWEEN ARTERIOSCLEROTIC ARTERIAL DEFICIENCY AND EXTERNAL VIOLENCE

Since arteriosclerosis is a process of slow development associated with advanced age, it is certainly not caused by injury but rather by the natural wear and tear of life. The effect of violence, therefore, is to aggravate the disease, and the background for this aggravation is the narrowing of the large and small arteries (arterioles) and the slowing of the circulation. An injury works harm in several ways. Generally speaking, a bruise or cut, by killing living cells, calls forth in the tissue the reaction of repair†. This

* Such comparison should be required by the court when the litigant alleges that a single foot or leg has had its circulation impaired as a result of injury. If the uninjured member shows precisely the same circulatory impairment, this speaks for disease as the sole cause, and against traumatic causation of impaired circulation in the one leg.

† The cause of this reaction is not settled. Possibly a specific chemical substance is released by the injured cells.

reaction is marked by an outpouring of blood and by the collection in the bruise, cut or lacerated part, of what is known as an exudate (serum, blood cells, fibrin) In the exudate, the process of disposal of dead and useless material goes on, in preparation for the laying down of the framework which is to replace and unite separated parts Uncomplicated repair of tissues other than bone normally requires eight to 12 days Its extent is, of course, related to the severity of injury and its success depends upon an active circulation and freedom from infection Blood must be carried in and worn-out material carried off by capillary * blood vessels hurriedly formed in great numbers to meet the emergency By contrast with the normal, the arteriosclerotic part has narrow, inelastic blood vessels carrying a restricted volume of blood at a slow pace Injury, then, is followed by failure of repair, or, if not by complete failure, by a process so slow as to be nearly useless In fact, the feeble circulation, barely adequate to meet the requirements of everyday life, is called upon for excessive activity to which it cannot possibly respond, and injured tissue suffers and even dies

Another adverse effect of injury is related to the choking of the local blood vessels by such exudate as is present, an accumulation of this material causing the familiar swelling of any bruised part Pressure within the injured tissues against all the blood vessels—both the arteries carrying blood to the region of injury and the veins carrying it away—acts most effectively upon the easily compressed veins As a result, blood can still enter the part but finds difficulty in leaving it, and so swelling increases, whereby a vicious circle of swelling and circulatory deficiency is set up, contributing materially to a total circulatory failure

Yet another bad effect of injury is related to the unhealthy state of the arterial walls Inelastic and poorly nourished, they are so easily injured that thrombosis † occurs within them Thus obstruction by a thrombus may cut down or altogether obstruct the blood supply of an injured part Should this occur in a large artery, in the region of the knee, for example, an individual previously believed to be in normal health might, for the first time, exhibit signs of a mild or serious arterial deficiency

The Evidences of Injury The evidence that external violence has aggravated an arteriosclerotic arterial deficiency is chiefly the changed appearance of the injured part

If a blow has been received, there will be some local swelling and an appearance of extravasated blood in the skin, that is, ecchymosis, but if the damage done by a blow is serious, the toe, toes or such part of the foot as is at and beyond the point of impact will soon turn purple and finally black The time required for this change varies The deep color will perhaps come first at the most distant point, probably within 24 hours, after which the black color of gangrene will often require several days to a week or more to

* There are tiny vessels having walls composed of a single layer of flattened cells The exchange of chemical materials between the blood within the capillaries and the tissue fluids outside them is very active

† In a previous note, the distinction between thrombosis and clotting is related

develop. Perhaps the part will hover, as it were, between life and death. Then, after many days of an appearance of purplish discoloration and swelling, some or all of it will take on the black color of gangrene. Only the tip of a toe may die, or the skin over a bony prominence. Ultimately, the gangrenous part, unless infection sets in, will shrivel or, as it is said, mummify. Thus injury may cause the loss of a toe, several toes, or even a part of the foot.

Pain, as a rule, is brought on or increased by injury in a part already the seat of arterial deficiency. The change of color in a toe or foot to deep red, reddish blue or deep purple, that is, the change showing aggravation of the deficiency, is usually accompanied by pain. Such pain is apt to be continuous, often preventing rest and sleep. It tends to be increased by elevation of the limb and to be lessened or relieved by depression. Since elevation diminishes the arterial supply to the part, and depression, by gravity, increases it, one must believe that it is through a further cutting down of the circulation that the injury causes pain. An arteriosclerotic individual, whose foot is rather pale and cool, may have been quite comfortable until an injury causes some part of the extremity to become discolored, painful and threatened with gangrene.

All such terminal stages of the disease may, of course, occur in the absence of violence, though usually some minor accident brings them on, as for instance, too close cutting of nails, paring off a callus or corn, or the irritation of an ingrowing toenail. If a bruise, abrasion, cut or laceration has occurred, however, even if of a minor sort, it may properly be blamed provided it can directly be connected with the part in which the disease has advanced.

Evidence that the ulceration or gangrene alleged to have been caused by an injury is due to aggravation of arteriosclerosis, rests upon the advanced age of the individual, a history of early symptoms of arteriosclerotic arterial deficiency, the various tests already described, especially the appearance of calcified vessels in the roentgenogram and lack of the normal arterial pulsations in the injured (and perhaps opposite) foot. Evidence of arterial disease in the opposite leg supports the contention of a previously existing arteriosclerosis, but apparent normality of the opposite leg does not disprove the contention.

If the injury is alleged not to have been the cause of swelling, discoloration and gangrene, that is, signs of serious arteriosclerotic arterial deficiency, it would be necessary to show that the advanced state of disease actually antedated the injury. That noteworthy effects due solely to arterial deficiency should appear suddenly and spontaneously as a coincidence with the injury is beyond probability.

That arteriosclerosis did not enter into the state of disease precipitated by injury would be indicated by the individual's age (below 55 years, as a rule) and the absence of calcification in the vessels of the injured limb, as shown in the roentgenogram. The fact, however, that in an individual of

an age consistent with arteriosclerosis no previous symptoms of arteriosclerosis had existed would not bar the diagnosis of arteriosclerotic arterial disease

One foot seldom exhibits an arterial deficiency without some sign of the disorder in the other, but differences between two extremities are very common, almost the rule. When an injury precipitates a serious situation in one foot it is, therefore, not remarkable that the second foot should show only slight signs of a defective circulation. Such variations are related to the patchy, erratic quality of the arterial narrowing in arteriosclerosis and to the vagaries of thrombus formation in the large and small arteries.

Injury of a Large Artery It has already been indicated that thrombosis in a large artery may bring on suddenly the signs of an arteriosclerotic arterial deficiency. An injury is capable of precipitating such a situation, to which the arteriosclerotic vessel is in any case liable. A case in point would be an unusual, sudden strain or blow from a heavy object acting upon the back of the knee or some part of the calf. As a result, there might be no ecchymosis or swelling, yet the effect of the injury upon the rather stiff, inelastic artery would be to set up an occluding thrombosis within it. The individual might, immediately or in a day or two, experience intermittent claudication (limp) or the toes and foot might in addition show the purplish color and coldness of a greatly restricted arterial circulation. In either event the pulses in the foot would be absent or greatly diminished in strength as compared to the opposite leg and the roentgenogram would almost certainly show some calcification in the vessels of the limb in question.

A popliteal aneurysm* (the main artery of the leg, in passing behind the knee, is called the popliteal), the most common non-syphilitic aneurysm, will produce a clinical picture almost identical with that of a thrombosis. Although it cannot be said that injury usually causes such an aneurysm which is really a partial rupture of the artery, it is probable that active bending of the arteriosclerotic vessel predisposes to it. Moreover, once the aneurysm is formed, heavy exercise or a blow may cause increased damage to the brittle wall of the aneurysmal sac and induce thrombosis within it. Though it is true that such may occur at any time, the relation of injury to a sudden increase in the size of the sack and to cutting off of the circulation from the leg beyond, might be convincing.

Cuts and Abrasions The rôle played by a cut or abrasion is similar to but not identical with that of a blow. Again an injury is made, calling for

*An aneurysm is a local dilatation of a large artery. It is not caused by injury. Certain aneurysms are due to syphilitic disease which weakens the arterial wall, which is then dilated by pressure of the blood stream. An injury or sudden strain may cause it to rupture, with a serious, even fatal outpouring of blood.

The popliteal variety is usually not syphilitic, nor is it due to injury, but since the artery is subject to a considerable amount of bending it may, especially if arteriosclerotic, crack, stretch or tear. Actually, one side "blows out" perhaps, allowing blood to escape. As this occurs, the blood, which cannot escape to the surface, becomes clotted and soon a false sack is found about it, the central part being more or less liquid. Since the mass pulsates with the arterial beat, it is detectable back of the knee by the touch. The vessels into which it is a surmountable obstacle receive a normal supply of blood, and thus a greater or less arterial deficiency results.

repair which is not forthcoming. A lifeless wound is left, which remains open and which almost necessarily becomes contaminated by bacteria. The infection may remain local, and indeed the neighboring tissues may establish an inflammatory zone about the injury, a feeble defense easily broken down. In some instances, appropriate treatment may cause the wound finally to heal, but the tendency is for the wound to become the source of a slowly spreading process marked by infection and death of the tissues. Neighboring toes, joints, indeed both bony and soft parts may become gangrenous. Frequently, in spite of treatment, loss of a leg is threatened. Because diabetes decidedly lowers the resistance of the tissues to infection, its presence should be suspected when a particularly feeble response to injury and infection is observed.

Thermal Injuries Exposure to Heat The effect of any application of heat to a part is to increase the rate of its metabolism, that is, its local chemistry. To support this locally increased activity, blood must be supplied freely. Should the arterial circulation be deficient, the heated tissues, failing to receive fuel to support their activities, break down. This may properly be called a burn, which occurs at a temperature lower than that at which this destructive reaction normally takes place. In other words, a degree of heat which vascular tissue would easily bear, harms or destroys avascular tissue.

Cold, as is now realized, up to a certain point, is well borne by tissues having a deficient circulation. The effect of cold is to retard metabolism, to slow down chemical processes. A cooled part takes on a dead-white appearance and becomes subjectively numb. When already near to gangrene and kept at a temperature barely above the freezing point, it suffers little harm from even prolonged exposure to such surroundings. When actually frozen, it dies, that is, sloughs, in medical parlance, but actually the conditions under which cold preserves a poorly nourished part or kills it are not precisely known. Nor is it known exactly under what circumstances cold, short of freezing, excites such contractions of the blood vessels of a vascular part as to damage it seriously. Individuals with a *normal* circulation may suffer marked contractions of small arteries as a response to cold, in a very chronic or obstinate form, and treatment, intended to relax such spasms before permanent damage can be done, is important. The ill-advised application of heat even to normal tissues which have been exposed to the constrictive action of cold is nearly as harmful as such application would be to tissues having a deficient arteriosclerotic circulation.

Economic Aspects of Arteriosclerotic Arterial Deficiency For both men and women, the early stage offers no economic hardship. The individual may not be able to walk fast or far and may require heavy foot coverings in cold weather, but long hours of standing cause no hardship.

As soon as discoloration and spontaneous pain set in—a frequent, prompt effect of injury—the individual is handicapped for any occupation requiring long hours of standing. If spontaneous pain is present, even a sedentary occupation requiring close attention may be impossible.

Ulceration and gangrene, with which pain is almost invariably associated, are totally disabling. It is difficult to conceive of any occupation, however trifling, at which the individual can work or to which he can give attention. Moreover, hospitalization is often though not invariably required, not necessarily for a long period, but to put the patient in the way of such treatment as will relieve pain, favor healing and perhaps permit ultimate local amputation, as of a toe. However, relief such that restoration to an active life and an occupation requiring normal vigor is secured cannot be considered probable. Such an event would be rare.

Amputation of a limb is often required. In that case, all of the leg below the knee will invariably be removed. Hospitalization for many weeks will be inevitable. A surgical fee must be added to the hospital expense. A determined person, otherwise well, will afterwards be able to secure and use an artificial leg, but, again, will be unable to resume an active, vigorous life, and the average individual will be unable even to use an artificial leg.

It will be seen that serious aggravation of the arteriosclerotic state by injury is likely to disable the individual, doing away with wage-earning at his or her original trade or occupation. In addition, hospitalization will usually be required, often for a considerable period. Amputation of a limb will call for prolonged hospitalization, a surgical fee and, in some cases, the expense of an artificial leg. Much of the disability is inherent in the age and lack of vigor of the injured person, that is, a disorder which would not disable a young or middle-aged individual usually disables the victim of arteriosclerotic disease.

THROMBOANGIITIS OBLITERANS BUERGER'S DISEASE

Although the veins as well as the arteries are involved in this disease, arterial deficiency is again the essential feature. The individuals attacked are far younger, however, than is the case with arteriosclerosis, and the disorder is capable of taking a greater variety of courses. The more elastic blood vessels of early life are able to establish new pathways, circumventing local arterial obstruction to a degree altogether beyond the capacity of the harder, older vessels of arteriosclerosis.

Thromboangiitis obliterans is almost exclusively a disease of males, so much so that this diagnosis, in any illness of a similar nature in a female, is accepted only after the most rigid scrutiny.

The disease is most apt to show itself in early adult life, that is, in the thirties and forties. However, it is not at all rare in the twenties, and has even been recognized in boys of fifteen to twenty. When the disease occurs in the sixth decade, a distinction from arteriosclerosis is difficult and of no great importance.

No cause is known. Some adverse influence of an inflammatory sort affects the blood vessels of the limbs, the legs primarily and almost exclusively. Seldom, and rarely in a serious form, it may involve the hands.

No actual infection has ever been proved, yet certain aspects of the disease suggest that something irritative and even destructive gains access to the blood vessels from the toes (and fingers) There is no question that tobacco smoking has a decidedly bad influence upon the course of the disorder, but this does not imply that it is necessarily a cause

Pathology The basic lesion is an inflammation of the walls of both arteries and veins of the limbs With this, as a natural consequence, thrombosis is invariably associated Vessels of medium size are the ones first involved Buerger maintains that the most characteristic, acute, inflammatory changes, marked even by occasional abscess-like collections of pus cells in the thrombus, are seen in the superficial veins, that is, those outside the muscular mass of the leg However, these superficial veins are involved in only about one-third of the cases It is probable that some good-sized artery (and vein) belonging to one of the three main, deep systems below the knee is first attacked Progressing in relapsing fashion with intervals of quietude, the thrombosis may extend in either direction, finally occupying the greater part of one or more of the three main trunks and even, in the most serious form of the disease, penetrating into the smaller vessels of the feet and toes In that case gangrene, very much like that of arteriosclerosis, sets in The thrombosing process need not necessarily obstruct completely the arteries and veins it involves Narrow channels are often left as the thrombus is converted into scar—organized, in medical parlance—but no vessel which is attacked ever again carries more than a small fraction of the original blood stream The tendency in the average case is to diversion of the arterial blood from the large and medium to the finer vessels or arterioles, a process which requires years Sometimes the femoral artery—the main vessel of the leg—is obstructed high up in the upper thigh, in which case the blood is often able to flow through newly opened channels about the blocked vessel and supply the peripheral parts through the relatively normal ones beyond Actually, as already stated, it is when the small vessels of the feet and toes are diseased that the condition is most serious, for then a collateral circulation cannot be established to supply these distant parts

Symptoms The disease is able, occasionally, to establish itself without causing any symptoms Pain is a late, never an early symptom, and even intermittent claudication on walking, the one characteristic early evidence of the disorder, need not be observed in persons pursuing a sedentary occupation As a rule, just as already has been told of arteriosclerotic vascular disease, the individual first notices a cramp-like sensation in the calf of the leg on walking This appears constantly when he walks for a particular distance at a particular pace so that one is accustomed to say that the painful lameness occurs after walking one or two blocks, or perhaps a quarter of a mile If the individual attempts to continue walking, the pain increases, finally involving the whole lower leg and radiating up the thigh If the victim sits down, however, or even stands still, the pain dis-

appears in a few minutes, and he can walk on as before. Hence the term "intermittent claudication," or "intermittent limp."

At this early but characteristic stage, which may persist for months or even years, the appearance of the affected limb—the two are seldom involved to an equal degree—is usually quite normal. If any change is evident, the foot and toes may appear a little pale. In that case, the individual will be apt to notice some slight feeling of coldness or even a tendency to "numbness" in the foot. Atrophy of the muscles, so common in arteriosclerotic arterial deficiency, is absent.

A later stage is marked by some degree of redness or blueness of one or more of the toes, especially the great toe. A part of the forefoot may even show the change, with which some slight swelling is apt to be associated. The discoloration is increased upon dependency and disappears on elevation, but in that position is succeeded by an unhealthy whiteness. At this time, spontaneous pain usually sets in. It has a disagreeable, burning quality, is apt to be made worse by elevation and diminished by depression of the limb. Even now, no ulceration or gangrene need be present, though both are threatened, and the subject is crippled. The affected foot is often sensitive to handling. Even in the absence of injury, the disease tends to progress. For dependency leads to swelling (edema), which in turn interferes with the already deficient blood supply of the part, a vicious circle.

A late stage is marked by actual ulceration or gangrene. The tip of a toe, a spot beside a badly curved nail, or over any bony prominence, often becomes deep purple and then black; or a small ulceration forms in one of these areas. The disorder is much like that of arteriosclerosis, though there is somewhat better resistance to infection. Pain, however, is decidedly more severe, persistent and disabling. If uncontrollable, pain rather than gangrene enforces amputation.

The course of thromboangiitis obliterans may be judged from the above account of the pathologic changes and symptoms. It is slow and subject to progress and recession. Fulminating cases are rare. Very chronic ones, marked by an intermittent limp in one leg, which persists for years without change, are not uncommon. Injury is very apt to lead to so rapid a development of the disease that it appears actually to have caused it, but ill-advised treatment of an "ingrowing" toenail or of a corn or callus is nearly as apt to be the exciting, aggravating factor.

A very interesting matter is the possible relation of the fungi of the skin and nails to the disease, that is, the dermatophytoses and onychomycoses, for which the layman's name is "athlete's foot." Certainly, secondary infections with bacteria are introduced through the desquamations, cracks and serious deformities of the nails due to these diseases. Conceivably, the tissues may become over-sensitive to the proteins of the fungus. In any case, treatment of serious infestation with fungi is valuable in a prophylactic way and influences favorably the course of the disease. Allusion has already been made to the relation of tobacco smoking to thromboangiitis obliterans. One often

sees a superficial wandering phlebitis heal and fail to recur as a result of withdrawal of tobacco, and occasionally a dramatic relief of pain

Considerable space has been given to an account of the pathologic changes, clinical symptoms and course of this rather common disease to bring out its capacity for latency, for periods of activity and quiescence and for responding, favorably or adversely, as the case may be, to a number of factors. These must be kept in mind in analyzing the effect of injury

In respect to evidences of a defective arterial circulation, reference should be made to the various tests described under arteriosclerotic arterial deficiency. In general, these tests are equally applicable in both diseases. The roentgen-ray, of course, will not reveal the calcification of the arteries characteristic of arteriosclerosis. But the colors in the skin, the reaction to elevation and depression of the limb, and the presence or absence of the arterial pulsations mean just what they do in arteriosclerotic arterial deficiency. Naturally, the comparative youth of those suffering from Buerger's disease makes the small vessels of their toes and feet more responsive to external temperatures, and thus the color of the toes often changes rapidly (and individually) as their surroundings vary between coolness and warmth. Such vasomotor effects are partly responsible for the "red, white and blue" toes of Buerger's disease

Aside from the appearance of inflamed thrombosed superficial veins in a small proportion of cases, there is no visible sign of the involvement of veins in the disease. The tests relate wholly to the state of the arteries

THE RELATION BETWEEN THROMBOANGIITIS OBLITERANS AND EXTERNAL VIOLENCE

The effect of a blow, crush, sprain or wound upon a limb, already the seat of thromboangiitis obliterans, is to bring out, rather dramatically in some cases, evidences of disease and to hasten its course. The failure of repair in response to injury when the arterial blood supply is deficient has already been explained. This occurs in Buerger's disease just as in arteriosclerotic states, and injured tissues become discolored, or partly gangrenous, or wholly gangrenous, according to the degree of arterial deficiency and the nature of the injury. Wounds heal badly and, in consequence, infection is threatened

Over and beyond such immediate effects as the above, the disease itself is decidedly aggravated. Let it be supposed that a man of 30, supposedly well, is injured by the dropping of the edge of a heavy box upon the base of his left great toe. The skin is not broken. He tries to continue work but finds the toe painful and gives up after a few hours. Beyond some black-and-blueness, the region of injury is little changed for a day or two, but soon the great toe becomes reddish-blue and increasingly painful. There is swelling of the toe and adjacent foot. In the course of a couple of weeks, a sore appears beside the toenail or the tip of the toe becomes black. Then

it is observed that the other toes are a little red, shiny and swollen. The adjacent foot shows a touch of this change. The man objects to handling of the toes and finds pain increased by elevation of the foot. Now perhaps it is noticed for the first time that the arterial pulses of the left foot are absent. To the touch, it is cool below the ankle. On elevation, the toes and foot appear a dead white. On depression, the toes, especially the great one, are purplish, the forefoot red, but shading upward into a normal color.

The state just pictured is a fairly advanced stage of Buerger's disease, brought on within a few days, and well developed within a few weeks, by a moderate injury. Perhaps an ill-advised attempt is made to amputate the partly gangrenous great toe, as a result of which a lifeless open wound is left. Even if healing occurs, the foot is left in some degree painful, the individual is crippled and cannot work. Thrombosis has probably spread from the region of injury by way of connecting blood vessels. Had there not been some background of disease present, the bruise would have healed after a short period of soreness, as most bruises do.

However, this may not represent the whole story. When the condition in the injured leg has been stabilized, a careful examination will be apt to show that the pulses in the second foot are weak—one of them may well have disappeared. There is often a suggestion that with the acceleration of the disease in one leg have been associated the first signs of trouble in the other. Just why this should occur—it need not—is far from clear. But it is a rather familiar observation that while an individual is confined to bed by a process of thrombosis ("phlebitis") in the veins of one leg, a similar process occasionally starts in the other. Something of the same sort may occur here.

Other injuries than a bruise are capable of producing similar changes. These include accidental wounds and abrasions as well as the cutting of corns or calluses and purposeful but ill-advised operative treatment of a deformed nail or toe. Such things should be inquired into in connection with the alleged incitement or aggravation of thromboangitis obliterans by injury.

The Evidence of Injury In the absence of other causes and even in the absence of any previously recognized symptoms, the appearance of reddish-purple discoloration and swelling, following within one or two to 10 days of an injury, indicates that a latent thromboangitis obliterans has been activated. Often a careful interrogation will, of course, disclose a story of earlier lameness on walking. The age of the individual will be of no great importance, provided it is under 50.

In addition to the color changes and disappearance of the pulses at the ankle, a study of the arterial oscillations in both legs will often be important. If a blood pressure cuff connected to an aneroid sphygmomanometer is firmly wrapped about the calf and inflated as if to record the blood pressure, the arterial beats will give a regular vibration to the indicator needle. The vigorous excursion of the needle in the normal person being known, a less

sened excursion in a case under study suggests strongly that the large arteries in the leg are in some degree obstructed by the disease

It goes without saying that, provided the individual has sufficiently recovered from the local disorder of the toes and can walk with reasonable vigor, the subsequent occurrence of the characteristic intermittent limp offers confirmatory evidence that Buerger's disease is now established

Evidence that the signs of disease, alleged to have been caused by an injury, are due to aggravation of thromboangitis obliterans, rests upon the appearance of the toes and foot (by contrast with the previous state), the prompt appearance of the changes and the incapacity of the individual. The arteries will not appear calcified by roentgen-ray. A normal state of the opposite leg does not deny the diagnosis of Buerger's disease, but diminished strength or absence of one or both of the arterial pulses in the opposite leg confirms the contention that the disease is present

If the injury is alleged not to have been the cause of swelling, discoloration and other signs indicative of the disease, it would be necessary to show that these signs had been present before the injury and had persisted without significant change. As in arteriosclerosis, it is beyond probability that noteworthy effects of thromboangitis obliterans should appear spontaneously as a coincidence with the injury

That thromboangitis obliterans did not enter into the disorder precipitated by the injury would only be indicated by the absence of characteristic signs of the disease in the injured leg, already described

Thermal Injuries Exposure to Heat and Cold To heat, the tissues in thromboangitis obliterans react just as do arteriosclerotic tissues, that is, heat calls for a metabolic activity for which a blood supply is not forthcoming. Thus, the terminal parts of the foot are readily injured by heat, the skin destroyed and ulceration established

Severe cold, that is, actual freezing, causes gangrene of the parts exposed. It must be supposed that, owing to the diminished arterial supply, frostbite under these conditions occurs more rapidly than is the case with normal tissues

Exposure short of freezing is likely to increase the contraction of the smaller arteries of the toes and feet. There is present in these vessels an element of irritability, that is, their muscular walls are readily thrown into spasm by cooling. This is an exaggeration of a normal reaction to cold already described, and indeed an excessive vasomotor irritability in response to cold is not by any means peculiar to thromboangitis obliterans. However, the effect of exposure to cold, if serious or repeated, is likely to aggravate the disease

Economic Aspects of Thromboangitis Obliterans The age of most individuals suffering from this disease holds out a promise of a considerable degree of recovery and some economic rehabilitation

The mild form of the disease, of which the only evidence will be intermittent claudication and lessening of strength in, or actual disappearance of

the pulses in the feet, limits the individual's ability to work to the extent that it lowers his capacity for locomotion, and for operation of a machine requiring active use of his legs. Moreover, it exposes him to aggravation of the disease by injury. Only in a small proportion of all cases is treatment able to remove such incapacity as is present.

The serious form, marked by purplish discoloration, ulceration and even gangrene of toes, can frequently be checked and improved, usually after a considerable period of treatment, a matter of many weeks and sometimes months. Let this be called "relief," not "cure." The younger the individual, the better the chance of recovery. Even the loss of several toes is consistent with a reasonably active life, though not with a strenuously athletic one. If relief for any reason is not obtained, the disease is totally disabling. Even if a limb is not lost, the persistence of a wearing pain renders the individual unfit to give his attention to an occupation requiring intelligence and care. Relief, however, seldom restores the individual to his previous full health. For one thing, he will seldom be able to walk fast or far, and he will never be able to run for any considerable distance. For another, he is susceptible to further accident and, consequently, to reactivation of his disease. He dare not engage in any hazardous occupation. On the other hand, he is free from pain, his general health is unimpaired, and he can give his full mind to his work, such as it is.

If relief of pain and ulceration is secured by amputation of a limb, the individual is fit only for a sedentary occupation. His amputation will leave him without a knee-joint in the amputated limb. Only an unusually determined person can lead an active life and never a strenuously athletic one. This is partly because the second leg is almost certain to be diseased in some degree. If both legs are seriously diseased, the individual must be held to be totally disabled, being fit only for such work as he can do in the house.

Relief of the disease is greatly at the mercy of the individual's eagerness for it and his determination to secure it. For example, if the painful period is prolonged, he may prove so lacking in resistance to pain as to have acquired a drug habit. Above all, if he will not abandon tobacco smoking, his disease will almost necessarily persist and indeed will probably be aggravated. Thus, the victim of thromboangitis obliterans whose disease is developed by injury may fail to seize an opportunity offered him for improvement and rehabilitation, a tendency which is emphasized by the demoralizing effect of the expectations of damages and insurance. Such considerations as the above are significant even when the treatment secured is ideal and not merely of average value.

MEDICAL FACTS THAT CAN OR CANNOT BE PROVED BY ROENTGEN-RAY; HISTORICAL REVIEW AND PRESENT POSSIBILITIES *

By SAMUEL W DONALDSON, M D F A C R , *Ann Arbor, Michigan*

INTRODUCTION

As the science of the practice of medicine has progressed, new discoveries have brought out newer methods of diagnosis and treatment. With the discovery of roentgen-rays by Professor Wilhelm Roentgen in 1895, an entirely new field was opened. The growth of this new field of medical radiology has been unusually rapid and of great importance. Radiology embraces the use of roentgen-rays, radium, and other radioactive substances. Roentgenology is a division of Radiology in that it is limited to the use of the roentgen-rays or x-rays, and medical roentgenology may be termed as the use of roentgen-rays for the diagnosis and treatment of diseases, deformities and infirmities.

In the development of this field of medical science not only medical specialists but also engineers and physicists have made many contributions. At first roentgen-rays were used to demonstrate the presence of opaque foreign bodies or broken bones in the human body. With the increase in efficiency in improved machines the pioneers in this new medical science began further experiments to determine the possibilities of this new invisible light. Experience and shrewd observation, combined with a knowledge of pathology, built up for them an ability to interpret properly the shadows they saw upon the finished plate. As the apparatus became more highly developed the technics of the roentgenologists also became more extensive and specialized. These men soon came to be recognized as specialists, and they formed organizations for the exchange of ideas and new procedures. Since that time, the practice of roentgenology has been, in the eyes of the medical profession, the practice of medicine.

Although it may be said that finished roentgen-ray films, properly termed roentgenograms, are merely celluloid records and that roentgen-ray machines are merely so much metal and oil and rubber, the essential element of medical roentgenology is the physician specialist. It is he who makes the examination, that is, directs the technical procedures and subsequently interprets the shadows on the finished photographic film. Those physicians and laymen who regard a piece of equipment as the answer to any given technical problem are laboring under a false impression.

ROENTGEN-RAYS AND THE COURTS

The knowledge gained from scientific discoveries soon makes its way into the courtroom as a means of bringing convincing evidence to the jury.

* Received for publication February 2, 1943

The study of finger prints and ballistics, for instance, has found a permanent place in administering justice in criminal cases. Chemists and toxicologists are often brought to court to present scientific facts before juries, and photographs had been used as secondary evidence long before the discovery of roentgen-rays.

One of the first suits in which roentgen-rays were introduced as evidence occurred in Nottingham, England, within four months after Roentgen's discovery. The first civil case in America in which roentgen-ray films were presented and admitted as evidence was that of *Smith v Grant*,¹ and the Haynes murder trial of 1897² was the first criminal case in which roentgen-ray evidence was introduced.³ The introduction of roentgen-ray films as evidence in personal injury suits is now practically the rule instead of the exception.

Conflicting points of view exist between the medical and the legal profession. Because the results of experimentation are uncertain and might result in unfair opinions, it is a function of the law to administer the kind of justice which has been arrived at through the experiences of the past. The medical mind has been trained for experimentation. Basically the legal mind leans toward tradition and precedent whereas medicine as a science is constantly discarding long used methods as newer and better ones are discovered. As a result, the law must be cautious in accepting new discoveries for, as has been stated, legal decisions are based on precedent. On the other hand, in the medical world the tendency is to swing towards a new treatment or method of diagnosis with unreasonable enthusiasm, perhaps only to find after a few years of trial that such method is not as efficacious as it was thought to be at the time of its introduction.

The first objection to the introduction of roentgen-ray plates as evidence was based on their inherent weakness and fallibility. Experts testified that no one knew anything about the new rays, and the courts ruled that juries should not be misled by something that was admittedly an experiment. However, within 20 years the courts treated the roentgen-ray as an authentic agent of medical science (*Prescott & N W Rd Co v Franks* (1914)).⁴ The trust which the courts place in the roentgen-ray today is illustrated in *Block v. Scibold*⁵ (1928), in which the Supreme Court of Wisconsin said "The physicians called by both plaintiff and defendant, when questioned as to what extent, if any, the injuries would be permanent, were practically agreed that no definite answer could then be made in that regard without at least having the aid of an x-ray picture." Although this opinion was rendered in a case involving bone injury, the principle may properly be applied to other phases of roentgenology.

¹ *Smith v Grant* (1896) 29 Chicago Legal News 115.

² *State v. Haynes* (1897), 50 Albany Law Journal 769.

³ *Prescott & N W Rd Co v Franks*, 111 Wis. 83, 103 S.W. 180 (1911) Ann. Cas. 1916 A, 77.

⁴ *Block v. Scibold*, 195 Wis. 111, 217 S.W. 681 (1928).

Every court in the land is clogged by numerous personal injury cases, and the State Compensation Commissions are always burdened with cases awaiting a hearing. Into these courts and before the Labor Commissioners there is a veritable parade of clients and their attorneys armed with roentgen-ray films, and accompanying them are those who are willing (for a fee) to testify as to the irrefutable evidence presented by the roentgen-ray, irrespective of the number or diagnostic quality of the films. Even the best trained roentgenologist cannot be expected to arrive at a satisfactory conclusion when he is confronted with an insufficient number of films of poor diagnostic quality. Although the courts are willing to accept properly authenticated roentgenograms in evidence as "pictures," they do not, it seems, ask the question, "A picture of what?" It should be apparent that having such a "picture" made and interpreted by some one qualified to do so is of the utmost importance. This principle, which can be applied to the interpretation of roentgen-ray films as well as to any other testimony of a scientific nature, was given in the celebrated and oft quoted case of *Ewing v Goode*,⁵ in which it was stated "when a case concerns a highly specialized art with respect to which the layman can have no knowledge at all, the court and jury must depend upon expert evidence."¹

The general tendency has been to refer to roentgen-ray films as secondary evidence. That is, they are not employed to prove conclusively that a certain condition existed at the time of injury or at the time they were made, but, rather, are used to aid the witness in explaining his testimony. In other words, the courts have transferred bodily to roentgen-ray films the rules of admissibility applied to photographs, maps, and diagrams, and the truth and accuracy of such films are protected by these rules. It should also be noted that roentgenograms are regarded as constituting a part of an objective rather than a subjective examination. This technical point of law is brought out in *Reeder v Thompson et al*.⁶ Therefore, the law has taken cognizance of the fact that by means of roentgen-ray machine the bones of the human body can be shown and that the "pictures" or roentgenograms may be admitted as evidence if they meet the rules of admissibility.

In order that it may be clear that the roentgen-ray is not the all-seeing eye but that correct interpretation of the shadows seen upon the roentgenogram must be made in order not to mislead the jury, the courts have repeatedly recognized the necessity of accurate portrayal of the parts to be examined and an accurate description of the findings. *City of Covington v Bowen*,⁷ *Stevens v Ill Cent Ry Co*.⁸ In *Vale v Campbell*,⁹ the Oregon Supreme Court recognizes the necessity of correct portrayal and expert interpretation. Numerous other decisions along this same line can be cited

⁵ *Ewing v Goode*, 78 F 442 (1897)

⁶ *Reeder v Thompson*, 120 Kan 722, 245 P 127 (1926)

⁷ *City of Covington v Bowen*, 191 Ky 376, 230 S W 532 (1924)

⁸ *Stevens v Illinois Cent R Co*, 306 Ill 370, 137 N E. 859 (1923)

⁹ *Vale v Campbell*, 123 Or 632, 263 P 400 (1928)

to show that the roentgenograms are the best available evidence of what they show, but wholly fail to convey to the ordinary layman the facts as they are actually shown unless interpreted by an expert roentgenologist

TECHNICS AND PROCEDURES

Discussion of the possibilities of the demonstration of disease conditions by roentgen-ray must keep in mind that what cannot be demonstrated today may be a more or less simple procedure in the future. The first medical uses of the roentgen-rays were, for example, to demonstrate the bones of the body and the denser structures and organs which cast a recognizable shadow on the fluoroscopic screen or on a photographic plate or film.² Important developments in technic have taken place during the years, and recently the roentgenologists have centered their attention more on the soft parts. The progress made in recent years without the use of contrast media seems due largely to the ultimate recognition that differences in density do exist which were formerly not noted or appreciated. Every roentgenologist has been able to see and interpret shadows on films heretofore unrecognized by him until some one who had made a special study of a particular condition had figuratively rubbed his nose in them. In order that these shadows may mean anything, medical knowledge must be brought to bear upon them. Obviously the diseases that do not produce differences in density, either actually or potentially—to be brought out by contrast media, are not amenable to diagnosis by roentgen-ray, as they cannot be shown on a film or as it is called a roentgenogram. Perhaps the best definition that can be given for a roentgenogram is that "it is merely a photographic record of the different densities through which the x-ray has passed."

Because the diagnosis depends on difference in density, the lungs naturally offered a peculiarly effective field in that many respiratory diseases occupy with a denser material, which is demonstrable, the normally air-filled spaces of the lung. Even though the early fluoroscopic screens were not very efficient, the movements of the heart and thorax were next to come under observation. Along with this, and as early as 1896 the pioneer work was done on the gastrointestinal tract where by the use of an opaque substance in a bag the esophagus and stomach could be visualized.² Subsequently a bismuth meal and then later barium were introduced as media for a complete study of the intestinal tract. Each year brings forth some new method by which an organ or condition heretofore not possible to demonstrate, can be outlined and any change from normal interpreted. For example, the injection of iodized oil or air into the spinal canal as a contrasting substance has increased the accuracy of the diagnosis of spinal cord tumors to an unpredicted degree.³

Measured quantities of air introduced into the ventricles and around the brain has become an essential examination to be employed for the benefit of the brain surgeon.⁴ Contrast media are also used to outline the extent and

size of fistulous tracts and to determine the existence of tumors of the breast⁵ or within the abdominal cavity,⁶ the patency of the Fallopian tubes,⁷ and the site of obstruction in bronchi.⁸ Also, by injection of a specially prepared dye into the blood stream the entire urinary tract can be seen,⁹ and the function of the gall-bladder can be shown by the administration of a drug either orally or intravenously.¹⁰ Another radiopaque substance may be injected into the blood stream, and by means of numerous films made in rapid succession the chambers of the heart, great vessels and their tributaries may be outlined.¹¹ Practically all of these procedures have been introduced within recent years, and research work is being conducted in order that newer methods of diagnosis can be perfected.

If one merely surveys an index of diseases and their complications, it becomes apparent that there are very few in which roentgen-ray is not of some help. The lesion may be demonstrated directly or indirectly by showing changes that are caused by that one particular condition. For instance, a dysfunction of the ductless glands of the endocrine system causes changes in the development of the bony skeleton or body as a whole.¹² Calcium deposits in the glands themselves can be shown and the ovaries and adrenals can be outlined by injection of air as a contrast medium into the abdominal cavity.^{13, 14} The thymus and thyroid and their size and shape, if abnormal, can be demonstrated without special technic.¹⁵ In other words, the disease of the ductless glands cannot always be demonstrated by roentgen-ray, but the results of their altered function are known and recognized by the well trained roentgenologist.

There never was and there never will be a perfect answer as to what possibilities exist for diagnosis with roentgen-ray examination. If the examination is done by the most competent available radiologist in the locality or the most competent available physician, there are no limits that can be expressed today that will hold for the future. If, however, the films are made and interpreted by any physician or surgeon who happens to have the case, there are such extensive limitations that it would require a treatise to list them all.

In the development of any paper directed towards evaluating criteria in the field of scientific proof as an adjunct to the field of evidence, it is timely to stress that on some occasions untrustworthy evidence may be accepted as final when in reality additional scientific evidence could have been obtained. In *Hollister v Robertson*¹⁰ (1923) the court said it was unwilling to follow its opinion in *Lasher v S Bolton's Sons*,¹¹ (1914), to the effect that the court was "without the power to require such an x-ray examination."

POSSIBILITIES AND LIMITATIONS OF DIAGNOSIS BY ROENTGEN-RAY

Keeping in mind that roentgenology is a rapidly advancing science and is subject to new discoveries, one may tentatively list those conditions which can

¹⁰ *Hollister v Robertson*, 208 App. Div. 449, 203 N. Y. (Supp.) 514 (1923)

¹¹ *Lasher v S Bolton's Sons*, 161 App. Div. 381, 146 N. Y. 321 (1914)

and which cannot be diagnosed by roentgen-ray today. In doing so, it is probably best to enumerate them according to their anatomical location. Since the fundamental precepts for roentgen-ray examination and diagnosis are that the shadows upon the film are records of density, either inherent in the body or introduced for the purpose of contrast, our first conclusion is that a diagnosis cannot be made if a difference in density cannot be demonstrated.

In listing the diseases, it is necessary to show, as a point in differential diagnosis, some of the conditions existing in a particular organ or part of the body that can be demonstrated in both its normal and abnormal state. Thus, the reasons why some conditions are diagnosable and why roentgen-ray examinations are not reliable in others will be disclosed.

Head. Injuries and diseases affecting the head are of great importance as it is there that the central nervous system and the control of the senses are located. A great number of industrial and automobile accidents result in head injuries and lead to litigation. At the present time it is a fair estimate to state that perhaps half of the fractures of the base of the skull are not easily and readily demonstrable by roentgen-ray. This is due to the fact that the line of cleavage is not separated widely and often occurs in a plane that is obscured by the overlying shadows of other parts of the skull. Body section laminography¹⁶—sectional radiography—has not yet been perfected to such a degree of accuracy that it is the answer to this problem of demonstration of basilar skull fractures. Another handicap in such cases is that when first seen, the patient is usually unconscious and incapable of full cooperation with the technician in making films in various projections. Roentgen-ray findings are usually negative in cases of concussion and in post concussion and post traumatic changes within the skull cavity.

Differentiation between fresh and recent fractures often presents a problem when a patient has had more than one head injury within a short time but when roentgen-ray examination follows the last injury only. Small subarachnoid hemorrhages, apoplexy and cerebral arteriosclerosis do not show sufficient changes to be amenable to roentgen-ray diagnosis. Occasionally some abnormality is shown in the roentgen-ray examination of the head of an epileptic patient, but even this does not offer conclusive proof that its existence is the cause of the epileptiform seizures. For this reason it would have little weight as evidence if it was alleged that the epilepsy was the direct result of any injury.

Teeth and Jaws. Thus far nothing has been said pertaining to roentgen-ray examinations of the teeth and jaws. The mandible and maxilla which may be considered in the same manner as other bones and subject to fractures, tumors and infections, are as easily accessible for radiographic examination and diagnosis as any other bone.

Dental roentgen-rays are a necessary part of every dental examination for the discovery of apical disease and unerupted teeth, and may be termed as imperative when searching for a focus of infection. Dental films have been introduced as evidence in court as a means of identification in criminal

actions when bodies could not be identified but when the shadows of the metallic fillings could be identified by the dental surgeon who had done the work upon the teeth. Diseases of the salivary ducts may be shown by injection of a contrast medium, and calculi in the glands themselves or in the ducts may be shown in the same manner as a calculus in any other part of the body.

Eye Non-opaque foreign bodies in the eye as well as soft tissue lesions of the eye ball and orbit are not demonstrable unless they have caused secondary bone changes. The cup shaped bony structure of the orbit precludes fine definition of the soft tissues of the eye and its various surrounding structures. Opaque foreign bodies in the eye can be detected and localized.

Nose and Throat Most conditions of the nose and throat, with the exception of the cavities of the nasal accessory sinuses, the middle ear and the mastoids, are diagnosable by direct observation by the examining physician. Although allergic rhinitis with edema of the mucous membrane of the structures may simulate, on the roentgen-ray film, the density of a pathological process within the sinuses, it can be differentiated from sinus disease by the clinical history, clinical findings, and sensitization tests. Here it may be said again, that, in many instances the roentgenographic findings are not always the last word, but are to be considered with other findings in arriving at a final conclusion.

Chest As has been stated, the heart and lungs drew the attention of radiologists in their early endeavors. The normal density of the structures and the readily demonstrable changes caused by the substitution of new densities when disease occurs, combined with the comparative ease of examination, particularly lend the chest to comprehensive study. Tuberculosis, pneumonia in its various forms, pleural effusions, and foreign bodies in the bronchi are all well publicized, and when such a condition is suspected, the laity consider the physician in charge of the case derelict in his duties if he does not include in his examination a radiological consultation.

Silicosis and the various pneumoconioses have received their share of attention within the last decade as a result of the enactment of laws declaring them to be among the industrial and occupational diseases for which compensation may be claimed, *Jones v Rinehart and Dennis Co*¹² (1933). The second and later stages of silicosis, asbestosis, anthracosis and similar conditions are diagnosable by radiological examinations, and, in addition, it can be determined by the same means whether or not another disease is superimposed.¹⁷

In respect to the medico-legal possibilities of inhalation occupational diseases and the possibility of post-war claims, if gas is used, one must consider the effects of noxious gases upon the mucous membrane of the tracheo-bronchial tree, in which the roentgen-ray findings are nil, although the patient may have severe, acute or chronic symptoms. Spray painters, using lead paint, are subject to lead poisoning which may be discovered by means of

¹² *Jones v Rinehart and Dennis Co*, 113 W. Va. 414, 168 S.E. 482 (1933).

clinical laboratory findings or demonstrated roentgenologically in other parts of the body. Spray painters using cellulose products do not show any lung changes roentgenologically. Fungus infections in the lungs resemble other acute respiratory infections. Diagnosis is usually confirmed by finding the specific organism in the sputum. Diagnosis by roentgen-ray of syphilis of the lung is doubtful.

Heart and Aorta A roentgen-ray examination of the chest does not mean that the person observed has had an examination of the heart even if the shadow of the heart is outlined upon the film. In some cases of heart disease and in congenital lesions the heart outline on the film will be an indication for further cardiac study. A complete examination of the heart roentgenologically is a special procedure done by tracing the heart outline by means of an orthodiagraph, or with films made in more than one projection at a distance to produce the minimum of distortion, conventionally seven feet tube-film distance. Calculation of the cardiac size is then made from measurements of the heart silhouette.¹⁸ Special examinations may be made by means of the kymogram, in which a grid moves across the film during a set interval of time, and the alterations in the markings caused by the movements of the heart are interpreted.¹⁹ All of these findings should be correlated with those of the electrocardiogram and clinical examination by means of the stethoscope. Special examinations of the heart and great vessels may be made, as stated previously in this paper, by injection of a radio-paque substance into the blood stream,¹¹ i.e., angiography, but the technic of such examinations is barely beyond the experimental stage and is not used under ordinary circumstances at the present time.

This experimental work has also shown that coarctation of the aorta—a congenital by-pass of the great vessels—of a minor degree can be shown by angiography whereas formerly the diagnosis was made from a scalloping defect in the ribs caused by a change in the collateral circulation of the inter-costal arteries.

Aneurysm of the aorta and aortitis may be diagnosed by roentgen-ray and can be differentiated from lung tumors, mediastinal masses, and other chest conditions by using films and fluoroscopy or in special cases the kymograph combined with the other two methods. Disorders of the pericardium are detected by the same roentgenographic procedures as are used for study of the heart and aorta.

Abdomen In listing those conditions of the abdomen which cannot be diagnosed by roentgen-ray, we must first turn our attention, as in other parts of the body, to the acute conditions. Acute appendicitis, acute pancreatitis, pelvic inflammatory disease and other acute infections do not always, and in many cases never, show diagnostic differences in density by the usual methods of examination. Any acute abdominal condition causing extreme pain and symptoms of shock should have the benefit of a survey film made in more than one position in an effort to detect the presence of free gas in the peritoneal cavity, thereby denoting that there has been a perforation at some

point in the gastrointestinal tract The absence of free gas in such suspected cases indicates that further study must be made to rule out coronary heart disease, bowel obstruction or any other acute abdominal condition producing prostration

In rupture or perforation of the liver or spleen, some roentgen-ray findings may be apparent, but they are certainly not convincing enough to make a positive diagnosis except in rare cases Diseases of the spleen which do not produce enlargement or cause areas of calcification cannot be classed as among those which can be diagnosed by roentgen-ray

Circulatory System Diseases of the blood stream involving the components of the blood are not at all dependent upon roentgen-ray for diagnosis per se However, positive bone changes in some of the hemolytic anemias, such as sickle cell anemia, may be some of the first noted changes in these cases The leukemias may present diagnostic roentgen-ray changes or findings which indicate further clinical laboratory study to confirm the existence of the disease Peripheral vascular diseases, varicose veins, and thrombophlebitis or obstruction of an artery, as well as of a vein, present no positive roentgen-ray findings in the usual examination However, by special examinations and the use of contrast media, worthwhile information may be gained

Examination in neurotrophic conditions which result in atrophy of the bones of the feet or hands, depending upon the extremity affected, such as Raynaud's disease, or tumors and injuries of the spine and Buerger's disease, i.e., endarteritis obliterans, a disease of unknown origin for which compensation has been claimed as aggravated by injury (*Hall v State Compensation Com'r*¹³ (1931)), show the bone changes but not those of the vessels even with soft tissue technic Roentgenographic examination for these and similar conditions of the peripheral vascular system may require a special procedure in which a radiopaque drug, used for pyelography, is injected into the blood stream and films made during the injection to show the course of the vessel and point of obstruction or narrowing By this same technic varicose veins and the collateral circulation set up around venous occlusion may be demonstrated²⁰

Bone and Joint Even though the bony skeleton and its joints have always been before the eye of the radiologist, many difficulties arise in this part of the body, which is the easiest to show roentgenologically Much attention has been given in recent years to the rupture of the nucleus pulposus of the intervertebral discs and the resultant changes which occur in the vertebral bodies Herniation of the disc into the spinal canal, associated with severe low back pain, may occur, and although definite evidence of rupture can be shown by roentgen-ray, a positive opinion that the herniation extends into the spinal canal cannot be made without the aid of a contrast medium, either air or iodized oil²¹

¹³ *Hall v State Compensation Com'r*, 110 W Va. 551, 159 S E 516 (1931)

Once again we must turn to the acute conditions and state that those involving bone are not readily diagnosable by roentgen-ray. The radiographic findings in acute osteomyelitis are negative, but every radiologist has had the experience of being severely criticized because he was unable to demonstrate evidence of bone infection within a day or so after the onset of the symptoms. Before a diagnosis of bone infection can be made by roentgen-ray, it is necessary to wait until there has been sufficient change in the periosteum or in the uniformity of bone density in that area to show that it is not normal. Another of the acute conditions which must come under consideration is the differential diagnosis between early joint tuberculosis and a recent soft tissue injury. Clinically the two conditions may be very similar, and only after sufficient lapse of time can the decision be made by roentgen-ray. Soft part injuries to joints are usually negative in routine examinations, but by special procedures certain findings can be demonstrated that are convincing evidence that injury to the cartilage and ligaments has occurred.

Crushing injuries to the vertebral bodies are not difficult to show, but linear fractures and injury to the articulating portions require painstaking technic. In other instances linear subperiosteal fractures are not demonstrable immediately after the injury but are easily discernible after bone absorption has taken place about the fracture. Small areas of malignant metastases in the bones are not always visible even though clinically they may be suspected. This is due to the fact that not enough change has occurred in the bone texture to be seen and the area involved may be obscured by overlying bone cortex. In those aged persons who are suffering from demineralization of the bones, especially the spine, it is exceedingly difficult to be positive whether the crushing of one or more vertebral bodies is the result of a recent injury or whether the crushed body existed before that time and the symptoms were merely aggravated by the injury.

Ordinary soft tissue injuries such as sprains, bruises, torn ligaments, and hematoma are not examined by roentgen-ray to show the injury but to rule out the possibility of a concurrent bony injury. Many of these injuries, especially hematoma, may show pathological changes after a lapse of time by a deposit of calcium in the hemorrhagic area. Myositis ossificans—calcium deposit in the muscle—is a frequent post traumatic finding when negative findings existed at the time of injury.

Probably the most common complaint of a large percentage of the patients seen daily in outpatient orthopedic clinics is low back pain. From the point of view of the compensation insurance claim adjuster, a low back pain, alleged to be the result of a most trivial accidental injury, is the most hazardous he is called upon to settle. The sacroiliac joint is subject to the same conditions as any other joint, namely, inflammation and trauma. The differential diagnosis between pain arising from the lumbosacral region, the lumbar spine, and the sacroiliac joint should be made by the examining physician by means of a careful history and physical examination; and then

he should confirm his findings by radiographic consultation. More often, though, the physician expects the radiologist to make the diagnosis without clinical findings. If the patient has lost time from work, he claims compensation because of disability, and he expects the radiologist to testify that his films show evidence of the injury. In the great majority of acute sacroiliac cases the roentgenograms are negative, but special procedures may be resorted to in an effort to bring out additional evidence. In chronic cases sufficient bone proliferation has occurred to indicate to the trained roentgenologist the pathologic lesion present. In some cases the clinical findings of sacroiliac sprain may be accepted in court in lieu of the roentgenographic findings (*Taylor v Southern Engineering Constr Co*¹⁴ (1930)), in which a physician expressed the opinion that a sprain of the sacroiliac joint severe enough to cause total disability, will not necessarily cause a widening of the bony relations or other bone injury sufficient to show in roentgenograms. The court in affirming the award for disability accepted the above testimony over that of a physician who had testified that a sacroiliac sprain could always be shown in the roentgenogram.

In addition to strains, sprains, torn ligaments, and other injuries not detectable by roentgen-ray, another question which often confronts the orthopedist or roentgenologist is that of arthritis of the spine aggravated by injury. There is no word in the medical nomenclature that is misused more often than the word "arthritis," nor is there any word that is more likely to befog the medico-legal picture. The term hypertrophic arthritis has been and is still being used relative to the marginal changes found about the bodies of the vertebrae, cervical, dorsal and lumbar. Arthritis does occur in the spine, but it must be remembered that it can occur only in true diarthrodial joints, and of these the only ones in the spine are those between the inferior articular processes of the vertebrae and the corresponding facets of the vertebrae below. The term hypertrophic arthritis as commonly used by physicians is a descriptive term of the changes found. When, however, it comes to the industrial or medical legal use of this term, it may become a cause of unnecessary cost to the defendant corporation or insurance company. It is generally accepted that lipping, spurs and marginal deposits are brought about by chronologic or anatomic age, or both, and are physiologic in nature. Obviously then, there can be no aggravation of these changes as they are normal healthy bone.²²

When one undertakes to state briefly what conditions, normal and abnormal, cannot be shown by roentgen-ray, he must immediately qualify that statement by adding "by routine examinations." Innumerable conditions that cannot be shown by the usual routine examinations can be very easily shown by a special technic or method. The simplest illustration of this is that stomach lesions cannot be shown by a film of the abdomen but are easily determined by a barium meal. A fracture which cannot be shown by routine examinations of the long bones can be brought into view by merely changing

¹⁴ *Taylor v Southern Engineering Constr Co*, 13 La. App. 292, 125 So. 877 (1930)

the position of the part to be examined from the routine position to a slightly oblique one

One of the perplexing problems that is often brought out in suits following non-union of fractures is whether or not there were soft tissues interposed between the fragments and whether the roentgen-ray would show such to be the case. In *Stoll v Balazs*²⁵ (1929), the court takes judicial notice of the question and answers it in the following words "There was evidence to show that it was the customary and usual practice to use roentgen rays in the reduction of fractures, and while they would not show a ligament or tendon between the ends of the fractured bones they would show that the bones had not been properly set so as to permit union" This may be a rather dogmatic statement in part, but the roentgenogram if carefully studied should lead one to be very suspicious of the possibility of the interposition of soft parts, and the subsequent treatment and observation should be carried on with this suspicion in mind

Genitourinary System In the genitourinary system practically every usual condition is amenable to roentgen-ray diagnosis. Some of the unusual conditions such as papillitis, carbuncle of the kidney, hemorrhagic nephritis, and their complications cannot be readily diagnosed. Rupture of the kidney may in some instances be diagnosed but not usually without the aid of contrast media. Dysmenorrhea, acute venereal infections, and early pregnancy are not within the province of the radiologist, although sterility due to obstruction of the Fallopian tubes and pregnancy in the later months are definitely radiologic problems. Abnormal positions of the fetus, abnormal development, single or multiple pregnancy, placenta previa,²⁶ and measurement of the pelvis to detect if deformities exist which will interfere with normal delivery²⁴ are now considered routine in many departments of roentgenology when a few years ago they would have been classified as special examinations. The sex of the child cannot be determined even though this is not an unusual question for the expectant parents to ask after a roentgen-ray examination.

Cerebro-Nervous System In respect to the nervous system, obviously pain cannot be shown, but in some instances it is possible to demonstrate the existence of muscle spasm, thereby indicating that pain to some degree may be present and in that way rule out the possibility of total malingering.

Most of the diffuse organic neurological conditions such as multiple sclerosis, familial degeneration of the spinal cord, amyotrophic lateral sclerosis, nerve injuries—especially those of the brachial plexus at birth—do not lend themselves to roentgen-ray diagnosis. Muscle atrophy and the sequelae of the above and similar diseases do, however, in time, show sufficient changes to be noted on the film.

Meningitis in its acute forms offers very little if any information by roentgen-ray. The same may be said of encephalitis with the exception of toxoplasmosis cerebri, which shows small calcified areas within the skull.

²⁵ 230 U. S. 1, 10 S. Ct. 107, 58 L. Ed. 722 (1929).

and it is by these characteristic shadows that the disease is diagnosable in infants²⁵

Gastrointestinal System Undoubtedly a chest study is the most frequently requested of all roentgen-ray examinations, with bone and joint second. Then perhaps come the gastrointestinal and abdominal studies. In examinations of the gastrointestinal tract the percentage of correct diagnoses of all conditions by a competent radiologist is very high and exceeds those of the clinician. The study of the gastrointestinal tract has become an art, and the recent investigation of the small bowel,²⁶ giving an explanation of various digestive disturbances, has opened a wholly unexplored field for the radiologist. Lesions of the esophagus, stomach and large and small bowel have always been studied by means of contrast media and under direct observation upon the fluoroscopic screen. At the present time one may list acute appendicitis, acute gastritis, acute peritonitis, and some of the local gastrointestinal parasites as not offering roentgen-ray as the method of choice for a diagnosis. Some intestinal parasites can be demonstrated by giving the patient a specially prepared meal and subjecting him to frequent observations in order to show that the parasites have ingested the opaque material.²⁷

Miscellaneous The acute fevers, typhoid, malaria, and other acute systemic infections and the acute exanthemata are not now subjected to roentgen-ray examinations at all. Whooping cough in late stages does show some pulmonary changes, but roentgen-ray is not necessary for diagnosis. Tularemia in some cases shows changes in the lungs,²⁸ and undulant fever causes bone changes, similar in respects roentgenologically to those caused by typhoid.²⁹ Inguinal and other hernias, unless large enough to contain bowel coils that can be seen when filled with barium or air, are not subject to roentgen-ray examination primarily for diagnosis.

Undoubtedly a large number of diseases and conditions have been omitted from this paper, as any cumulative index of radiological literature will show. But at least it has been an attempt to show the fundamental requirements for this type of consultation and its value in medico-legal work. Many patients for whom roentgen-ray would be an aid in diagnosis are seen each month by physicians who are uncertain whether or not roentgen-ray would be of value. The radiologist and pathologist occupy a unique position in the medical world as they are dependent upon referred patients, and a very good slogan for physicians to adopt is that "When in doubt, ask your radiologist."

For instance, any injury or disease involving bones or joints of the human body, is from a diagnostic standpoint a radiological problem. In *James v Grigsby*¹⁶ (1923), *Taylor v De Vaughn*¹⁷ (1928), and in numerous other cases the decision of the courts has been that the physician in attendance was negligent in that he did not use roentgen-rays in the diagnosis and treat-

¹⁶ *James v Grigsby*, 114 Kan 627, 220 P 267 (1923)

¹⁷ *Taylor v De Vaughn*, 91 Cal App 318, 266 P 960 (1928)

ment of a fractured bone. Scientific proof, such as roentgen-ray film, of the absence or existence of disease or injury is obviously required by the courts rather than a diagnosis made from clinical findings alone.

In certain localities and in certain clinics of this country radiologists have made a special study of some particular conditions and have reached a high proficiency in the diagnosis of that disease. Among the more prominent are the radiographic diagnosis of early carcinoma of the breast and its differential diagnosis from benign tumors³⁰, silicosis and allied inhalation diseases (especially by those radiologists in the mining and quarry districts)³¹; coccidioidal infections (on the Pacific coast)³², and those conditions which are more prevalent in certain parts of this country. This also holds true for the radiologists of foreign countries, who have the opportunity of seeing those conditions which are peculiar to their own geographic location, and in the diagnosis of which the radiologists of other countries would be on unfamiliar ground.

PREDICTIONS

Taking into consideration the rapid advances made by roentgen-ray in the past, one cannot but be optimistic about the many possibilities for diagnosis that this branch of medicine may produce in the near future. The successful results that have been attained by the development and perfection of various dyes for demonstration of the kidney and gall-bladder should stimulate investigation for further study of the glands of secretion. It is perfectly possible that there may be developed a chemical substance which would be electively secreted with the pancreatic juice, and such a procedure would undoubtedly shed some light upon the function of that organ and add to the now meager knowledge of diabetes. Even now it is possible, by selection of the kidney dye with the proper chemical formula, to determine whether the pathology in the kidney involves the glomeruli or the tubules³³.

Science has made a great step forward in the development of the electron microscope, and it is not outside of the realm of investigation in light amplification that some one may perfect a fluoroscopic screen that will enable the radiologist to see objects of fine structure which he cannot now distinguish at all because he looks upon the screen with poor eye accommodation³⁴.

The radioactive substances produced by the cyclotron and the peculiar affinity of these substances for various tissues, such as radioactive iodine for the thyroid, phosphorus for bony structures and other elements now under investigation present innumerable possibilities³⁵.

All of these changes will and must be accepted by the courts as other scientific discoveries have been accepted in the past, and toward an aid in scientific proof along this paper has been written.

BIBLIOGRAPHY

1. *Journal of the American Medical Association*, 1937, Ch. C. I. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100.

- 2 GLASSER, OTTO, Editor The science of radiology, 1933, Chas C Thomas, Springfield, Illinois
- 3 YOUNG, BARTON R, and SCOTT, MICHAEL Air myelography, Am Jr Roentgenol, 1938, xxxix, 187-192
- 4 PANCOAST, HENRY K, and FAY, TEMPLE Encephalography Roentgenological and clinical considerations for its use, Am Jr Roentgenol, 1929, xxi, 421-447
- 5 HICKEN, N F, BEST, R R, HUNT, H, and HARRIS, T T The roentgen visualization and diagnosis of breast lesions by means of contrast media, Am Jr Roentgenol, 1938, xxxix, 321-342
- 6 SANTE, L R Principles of roentgenological interpretations, 1942, Edwards Bros, Ann Arbor, Michigan
- 7 JARCHO, JULIUS Gynecological roentgenology, 1931, Paul B Hoeber, New York
- 8 FARINAS, P L Recent progress in the bronchographic examination of bronchogenic carcinoma, Am Jr Roentgenol, 1940, xlv, 370-385
- 9 NICHOLS, B H, and LOWER, W E Roentgenographic studies of the urinary system, 1933, C V Mosby Co, St Louis, Missouri
- 10 GRAHAM, EVARTS A, COLE, W H, MOORE, SHERWOOD, and COPHER, G H Visualization of the gall-bladder by the sodium salt of tetrabromphenolphthalein, Jr Am Med Assoc, 1925, lxxv, 953-955
- 11 ROBB, G P, and STEINBERG, I Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man, Am Jr Roentgenol, 1939, xli, 1-16
- 12 ENGELBACH, W V Endocrine medicine, 1932, Chas C Thomas, Springfield, Illinois
- 13 STEIN, I F Eight years' experience with roentgen diagnosis in gynecology, pneumoperitoneum and lipiodol in pelvic diagnosis, Am Jr Obst and Gynec, 1931, xxi, 671-679
- 14 GIANTURCO, C, and DRENCKHAHN, C H The role of perirenal injections of gas in the radiological study of the adrenal glands, Radiology, 1938, xxx, 500-504
- 15 PANCOAST, H K Roentgenology of the thymus in infancy and differential diagnosis of enlarged thymus and its treatment, Am Jr Med Sci, 1930, clxxx, 745-767
- 16 MOORE, SHERWOOD, and CONE, A J Body section roentgenography as diagnostic aid to otolaryngology, Surg, Gynec and Obst, 1941, lxxii, 514-522
- 17 PANCOAST, H K, and PENDERGRASS, E P Roentgen technic with especial reference to examination to diagnosis to exclude silicosis, Jr Indust Hyg, 1934, xvi, 165-173
- 18 KURTZ, CHESTER M Orthodiagraphy, 1937, The Macmillan Co, New York, N Y
- 19 SCOTT, W, MOORE, S, and McCORDOCK, H A Roentgen kymographic studies of cardiac conditions, Radiology, 1937, xxviii, 196-208
- 20 EDITORIAL The early diagnosis of venous thrombosis by venography, Am Jr Roentgenol, 1942, xlvii, 469-470
- 21 CHAMBERLAIN, W E, and YOUNG, BARTON Air myelography in the diagnosis of intraspinal lesions producing low back and sciatic pain, Radiology, 1939, xxxiii, 695-700
- 22 GEORGE, A W (Editorial) The use and abuse of the term hypertrophic arthritis relative to marginal changes in the vertebrae, Radiology, 1941, xxxvi, 745-746
- 23 UDE, W H, WEUM, T, and URNER, J A Roentgenologic diagnosis of placenta previa, Am Jr Roentgenol, 1934, xxxi, 230-233
- 24 BALL, ROBT P Pelvicephalometry, Radiology, 1938, xxxi, 188-196
- 25 DYKE, C G, WOLF, A, COWEN, D, PAIGE, B H, and CAFFEY, JOHN Tumorplastic encephalomyelitis, Am Jr Roentgenol, 1942, xlvii, 830-844
- 26 GOLDEN, ROSS Abnormalities of the small intestine in nutritional disturbances Some observations on their physiologic basis, Radiology, 1941, xxxvi, 262-286
- 27 MORTON, C B, and ARCHER, V W Ascariasis some surgical and roentgenologic aspects, Jr Am Med Assoc, 1932, xcvi, 473-476
- 28 WINTER, M D, FARRAND, B C, and HERMAN, H J Tularemia, pulmonic form, report of 4 recoveries, Jr Am Med Assoc, 1937, cx, 258-262

- 29 BISHOP, W A, JR Vertebral lesions in undulant fever, Jr Bone and Joint Surg, 1939, xxi, 665-673
- 30 LOCKWOOD, IRA H Roentgen-ray evaluation of breast symptoms, Am Jr Roentgenol, 1933, xxix, 145-155
- 31 COLE, L G, and COLE, W G Pneumoconiosis, 1940, John B Peirce Foundation, New York, N Y
- 32 CARTER, RAY The roentgen diagnosis of fungus infections of the lungs with special reference to coccidioidomycosis, Radiology, 1942, xxxviii, 649-659
- 33 PENDERGRASS, E P Excretory urography as a test of urinary tract function, Radiology, 1943, xl, 223-246
- 34 CHAMBERLAIN, W E Fluoroscopes and fluoroscopy, Radiology, 1942, xxxviii, 383-413
- 35 HEMPELMANN, LOUIS H, JR (Editorial) The cyclotron and its medical implication, Radiology, 1942, xxxix, 627-628

CRIMINAL INTERROGATION WITH THE LIE DETECTOR; EIGHT YEARS' EXPERIENCE BY THE MICHIGAN STATE POLICE*

By LE MOYNE SNYDER, M D, *East Lansing, Michigan*

DURING the era since the last war the science of criminal investigation has enjoyed tremendous growth. This quarter of a century has witnessed the development of fingerprinting into a common, everyday procedure. Scientific firearms identification (improperly called "ballistics") is a development of the last few years. The employment of blood grouping examinations in cases of contested paternity, scientific determination of alcoholic intoxication and many other valuable procedures have all come into use during this same time. The medical profession can take pride in the fact that its members have contributed so generously to the development of this new field.

Probably the most spectacular instrument devised in this era is the lie detector. In localities where it is in common use it has provoked enormous public interest. The idea of being able to detect a liar by means of a machine is fantastic to the uninformed. Many scientifically trained persons who have not yet had the opportunity to see it in actual operation still regard it as a mixture of voodoo and hokum. The Michigan State Police for the past eight years have employed one of the better known lie detectors, the Keeler polygraph. Although other types of apparatus have also been employed from time to time, the results obtained with the polygraph have been the most satisfactory. However, the fact that the series of cases reported here is based on results with the polygraph should create no inference that there are not other makes of apparatus which will give satisfactory results.

For thousands of years attempts have been made to establish guilt or innocence by such procedures as the trial by ordeal, and its more modern counterpart, the "third degree." These found expression in an infinite variety of cruelties and were only uniform in expressing the frustration felt by the prosecutor and police. Under this system many guilty escaped, many innocent confessed, and all were mistreated.

Physiology Involved When most persons deliberately tell a falsehood certain physiological reactions take place. These may exhibit themselves as blushing, dryness of the throat, swallowing and many other ways. Following the pioneer work of Lombroso¹ Marston, Benussi, Larson and others, Leonarde Keeler in 1926 developed the polygraph. On a moving strip of paper this instrument records simultaneously changes in the blood pressure and changes in depth of respiration. Earlier investigators had noted that

* Received for publication February 8, 1943

¹ LOMBROSO, C. *L'homme criminel*, 2nd ed, 1895, 1, 330-346

immediately following the telling of a lie the blood pressure rose and soon fell again to approximately normal

Likewise, it was apparent that during the telling of a lie and for a short time afterwards respirations were apt to be shallow. A period of shallow breathing was usually followed by extraordinarily deep respirations in an endeavor for the subject to recover his breath. Consequently by inter-

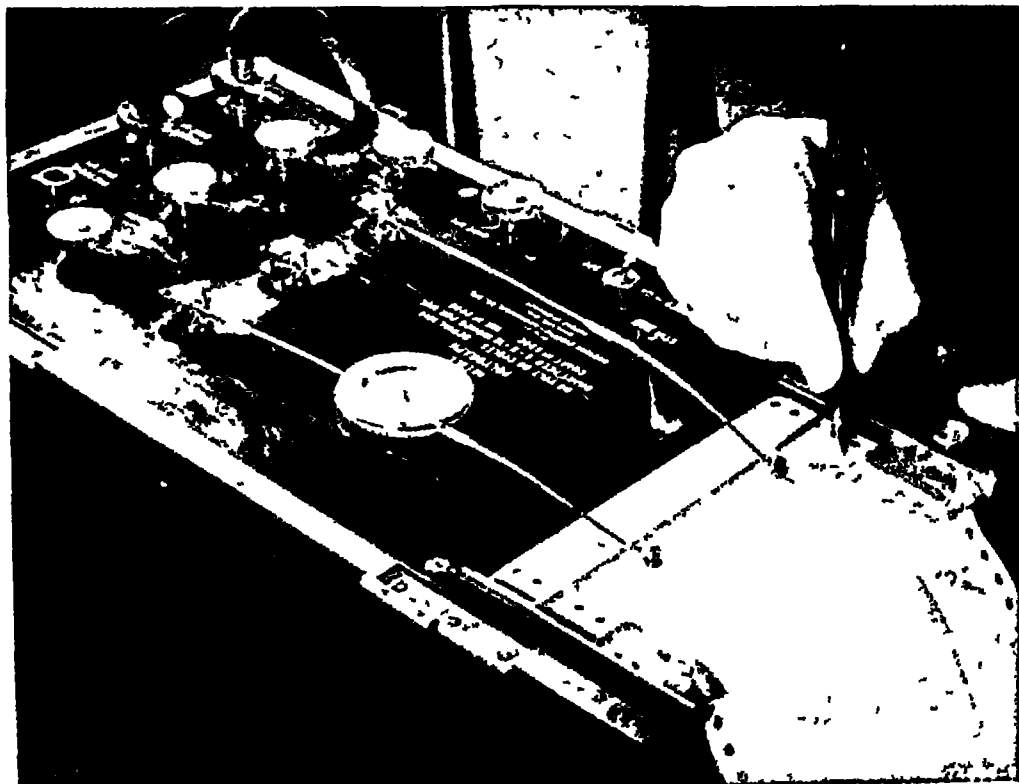


FIG 1 The polygraph in operation. The operator makes an "x" at the point on the record at which the question is asked. Next to the operator's hand is the pen that records the blood pressure while the other one registers depth of respirations.

persing the questions which are directly related to the crime with questions which have no bearing on the subject under investigation, it is possible to throw the significant changes into bold relief. For instance, a typical series of questions might be something like this:

- 1 Did you have breakfast this morning?
- 2 Do you smoke?
- 3 Do you drive a car?
- 4 Did you shoot John Doe?
- 5 Do you live in Michigan?
- 6 Do you know who killed John Doe?
- 7 Is today Thursday?
- 8 Have you lied in any of these answers?

resistance of the subject during questioning. It is attached to the hand of the person being questioned and is of value in some cases. This unit has been used in only a few of the cases reported here.

The reaction of most persons is quite uniform when first informed of the lie detector and its method of operation. They express themselves usually about like this: "If I were ever put on the lie detector I would be so nervous that I am sure my reactions would indicate that I was guilty even if I were innocent." Fortunately such is not actually the case. Practically all persons exhibit some nervousness when first run on the polygraph. The experienced operator can detect this easily and make proper allowances for it. As a matter of fact, the records are very barren of innocent persons being unjustly accused by reason of their polygraph tracings. In our own experience, we know of no such case.

The next question is quite apt to be "Is the machine infallible?" That question is exactly like asking whether a clinical thermometer, stethoscope, roentgen-ray machine or compound microscope is infallible. A trained scientist may be mistaken in what he sees or hears by any of these devices. Like the thermometer and stethoscope the polygraph is simply an instrument for noting or recording physiological processes and it is possible for the operator to be mistaken in his interpretation of the recording. Even in the best of clinics the interpretation of roentgen-ray film is not 100 per cent accurate, but that does not imply that the machine should not be used. The same can be said for the polygraph.

There are two essential requirements for the successful employment of the lie detector: first, a competent operator, and second, a proper place in which to conduct the examination.

What should be the background and training of a person who is to conduct polygraph cases? The first essential is that he have a long experience in criminal, business, social, and professional matters. In other words he must know how "the world operates." He must combine a scientific approach to his problems with complete and absolute honesty. The temptation to indulge in wishful thinking in the interpretation of polygrams is often great. The requirement of the operator to interpret the tracing as it actually is, rather than as what he hoped it would be, is basic. When such a person is properly trained in the use of the apparatus he should make an excellent operator. A medical training would often be helpful but is by no means essential.

In what surroundings and under what conditions should a lie detector test be given? When the Michigan State Police started using the polygraph eight years ago, it was frequently taken all over the state and tests run on subjects in county jails, prosecutors' offices, or any vacant corner that seemed to be convenient. It soon became apparent that this was a mistake. The general excitement and confusion present usually made it impossible to run a satisfactory test. Furthermore, there was a distinct tendency on the part of the local police officers to substitute the lie detector for an adequate in-

vestigation from the police angle To attain any degree of success with the instrument, it is necessary for the operator to have all of the procurable facts with respect to the subject prior to the test Consequently when suspicion is directed toward an individual in connection with a crime, he should not be subjected to a polygraph examination until the police have completed an exhaustive inquiry into the crime and all related facts

When it became apparent that this method of conducting an examination was unwise, a special room was constructed at the headquarters post in East Lansing This room is situated in a quiet section of the building and is sound proof The walls are decorated, the floor carpeted, comfortable furni-



FIG 3 Questioning a subject on the lie detector This shows the new electrodermal response unit attached to the subject's left hand and recording on the middle pen of the instrument The pneumograph tube is adjusted around the chest and the blood pressure cuff about the right arm The operator is Detective W M Petermann and the subject is posed by Detective Don Berry of the Michigan State Police

ture has been installed, and everything done to produce a quiet, restful atmosphere without unnecessary fixtures and pictures which will distract the attention of the subject No officers in uniform are present and the atmosphere is that of a quiet, business-like office

After reviewing the case with the officers, the operator discusses the matter privately with the subject The purpose of this is to enable the operator to determine the precise points of conflict between the accused's story and the available evidence The interview also serves to impress the subject that he will be fairly and civilly treated

Technic of the Test By the very nature of the examination the full consent and cooperation of the subject is required. There is no possible way to force a person against his will to submit to an examination. To try to do so would be precisely like attempting to get a satisfactory electrocardiogram on a hostile and recalcitrant individual. Consequently the "third degree" and the lie detector technic represent opposite extremes in criminal interrogation. Any show of bodily violence, threatening, shouting or abusive language preclude any success with this apparatus.

The manner in which the test is conducted is explained to the accused. He is told that he will suffer no pain more than the slight discomfort from the blood pressure cuff about his arm. After the subject has consented to take the test he is taken into the examination room and seated in a straight chair with the apparatus placed behind him. The chair should be equipped with wide arms so that he is perfectly comfortable.

All the questions asked can be answered by a simple "yes" or "no" and the person examined is told to reserve any explanations or qualifications of his answers until the test is completed.

The blood pressure cuff is then applied and the pneumograph tube is adjusted around his chest. The instrument is then started and recordings made of his blood pressure and respirations for a minute or so with no questions being asked. This is to allow the fluctuations in these recordings due to nervousness and anxiety to subside.

The subject is then given a numbers test. This is done by showing him 10 cards numbered from 1 to 10. He is told to select one of the numbers and keep it in his mind but to lie about it when he is asked if that is the number which he has selected. In other words, the subject is to answer "no" when each card is presented to him. The instrument is then started and each card is shown to him slowly and he is asked if that is the card he has selected. Of course he answers "no" to all of these questions including that on the number he has chosen.

The purpose of this test is to see how he reacts under actual questioning and to record his response on the blood pressure and pneumograph tracing when he lies. There is seldom much difficulty in determining the number chosen. This test also has a certain psychological value by impressing upon the subject that it is possible to tell by means of the apparatus when a person is evading the truth.

Following this, he is asked a series of 7 to 10 questions which deal with the crime itself as previously outlined. Questions dealing directly with the crime are interspersed with those of an irrelevant nature. After this test is run the pneumograph tube and the pressure cuff are loosened and a short rest period allowed. The test is then usually repeated once or twice more using different irrelevant questions and placing the pertinent questions in a new order. When these tests are completed the operator usually is convinced that the subject has guilty knowledge of the crime or is entirely innocent. (Because, however, the tracing may be of such a nature that the

operator can arrive at no definite conclusion with respect to the guilt or innocence of the suspect

There are many conditions which may contribute to the making of a tracing upon which no analysis can be made. The subject may be of such a low intellectual caliber that he has no normal responses to questions of guilt or innocence. Such conditions as an uncontrollable emotional reaction or a bad cough may cause considerable difficulty. Organic conditions such as hyperthyroidism, auricular fibrillation or other circulatory diseases will cause difficulty in the interpretation of the tracings. However, it is extremely difficult for a person who is physically normal to run an innocent tracing when he has guilty knowledge of the crime. In fact the harder he tries to, the more pronounced the guilty response is likely to be.

TABLE I
Polygraph Cases Conducted by the Michigan State Police

	Cases	Subjects	Tests	Admissions	Guilty Knowledge	Cleared	No Analysis
1935	92	165	660	41	54	96	15
1936	88	197	591	20	26	43	19
1937	75	107	381	23	44	57	6
1938	127	233	485	69	104	125	4
1939	153	222	354	49	98	111	12
1940	145	235	465	39	75	155	5
1941	121	239	545	33	72	156	11
1942	104	153	473	34	90	60	3
TOTALS	905	1551	3954	308	563	803	75

Results of the Lie Detector Test The above table shows the results in the use of the polygraph on 1551 subjects over a period of eight years. All of these tests were conducted by either Captain Harold Mulbar or Detective W. M. Petermann. On 563 subjects the instrument gave an indication of guilty knowledge, and in 308 of these cases an admission was obtained at the completion of the test. In 803 cases the subject was cleared as having no guilty knowledge of the crime and in 75 cases the tracings were of such a character that no definite analysis could be made.

In a table of statistics such as shown above there are of course some unknown quantities. One might ask "How about those subjects on whom the instrument indicated guilty knowledge but from whom no admission was obtained?" Some of these were tried and convicted, others were found not guilty and some were not brought to trial. *However, a much more important fact is that in no case in which the instrument indicated that the subject had guilty knowledge of a crime have later events proved an erroneous conclusion was drawn.*

A similar question might be raised as to the 803 persons who were cleared by the polygraph. In many of these cases the diagnosis of innocence was substantiated by the subsequent confession of other persons. In only

one instance out of this series did the operator conclude that the subject was innocent and later have him confess to the crime. Upon subsequently reviewing the graphs, the operator acknowledged that the indication of guilt was there but the error lay in the interpretation of the tracings.

Interpretation of Cases Occasionally it happens that a person is innocent of the crime about which he is being questioned but has committed some other offense which disturbs his reactions. For instance, a truck driver was brought in for an examination, who was accused of having stolen funds that he had collected on his delivery route. At the interview prior to the polygraph test he stated that he had a wife and three children. During the test, when questioned with respect to the missing money, he ran a perfectly clear record but showed a great deal of disturbance at the supposedly irrelevant question "Are you married?" The question was repeated several times with similar results. When questioned with respect to his marriage it developed that he never had been married to the woman with whom he was living and who was the mother of his children. He stated that they always had intended to get married but had neglected to do so until the arrival of the children made it impossible.

During the last eight years that the lie detector has been in use by the Michigan State Police one of the striking advantages it offers is in the clearing of innocent persons. There have been several instances in which the evidence against a person was so strong that he probably would have been convicted had the case gone to trial. Boichard² has pointed out that persons who are entirely innocent of wrong doings are occasionally convicted of serious offenses.

Some time ago a salaried employee of the state received his pay check and left to spend the Christmas holidays at a small town in Minnesota. When he returned to Lansing about two weeks later, he reported that he had lost the pay check and requested that another one be issued. In due course a duplicate check was given to him and the matter forgotten. A year later, while he was spending the holidays in the same Minnesota town, the original check was cashed, the only alteration being that it was dated a year later. The cashed voucher returned to Lansing before he got back and when he arrived he was placed under arrest. Of course he protested his innocence, but the fact that the check had been cashed in the same small town in which he was known to be at the time, and in which he had not been for a year, made a strong case against him. Even the endorsement appeared to be his.

On the polygraph this man ran a completely innocent tracing and on the strength of that alone he was released. A few weeks later the truth of the matter became known. The check was lost as he had contended and fell into the hands of a man who had exactly the same name. He held the check for several months, finally altered the date of the year, endorsed and

cashed it. The fact that the state employee happened to be in the town at the same time was pure coincidence. Enough similar experiences have happened to warrant the conviction that the polygraph is a great source of protection to the innocent person.

Likewise, the apparatus is of great aid to the police when the evidence against the suspect is rather weak but the polygraph shows he has guilty knowledge of the crime. Even without an admission it gives an incentive to the police to keep working on the case until more evidence is uncovered. In the experience of the Michigan State Police many cases have been followed through to a successful conclusion, which undoubtedly would have been dropped early in the investigation had not the polygraph convinced the officers they were on the right track.

Status of the Polygraph in Court Inbau³ in his recent book "Lie Detection and Criminal Interrogation" has completely covered this topic. Only a few attempts have ever been made to introduce polygraph evidence in court. In Michigan no direct attempt has ever been made to introduce this type of evidence. The occasion seldom arises when such a move is necessary or even desirable. Although the instrument has definitely proved its worth, still there are no set standards for either apparatus or operators. Consequently it is apparent that one fiasco in court might retard the successful use of the device for many years. The lie detector is not an instrument that can be turned on and played like a phonograph. It is simply one useful aid to the criminal interrogator, yet the attempt is usually made to put the polygraph rather than the operator on the stand. In court it is like trying to examine a microscope rather than the pathologist. After more years of experience have been accumulated with this device and standards of technic have been established, it may be possible for trained criminal interrogators to give an opinion as to guilt or innocence partially based on lie detector recordings.

CASE REPORT

On December 1, 1942, a report came to the East Lansing detachment that Mrs. Ellen Pitts was missing and a routine investigation was started. The investigators learned that Mrs. Pitts was married, mother of four children, and a few weeks earlier had deserted her family who lived on a farm near Morrice. The investigation also disclosed that she was keeping company with Harland Nevins, aged 28, married and father of four children, living at 528 South Detroit Street, Lansing Township. Nevins had bought a homemade house-trailer situated in an abandoned clay pit about a half mile from his residence and there had installed Mrs. Pitts.

On being questioned by the police Nevins asserted that he had not seen Mr. Pitts for a week or so but thought that she had obtained a job as a domestic. The trailer was searched and everything found to be in order.

On December 8 Mrs. Nevins came to the police post and said that her husband while intoxicated, had told her that he had shot and killed Mrs. Pitts and buried her in a hole that he had dug in the back yard of their home on Detroit Street. She

³ INBAU, FRED E. Lie detection and criminal interrogation, 1942, The Williams & Wilkins Co., Baltimore.

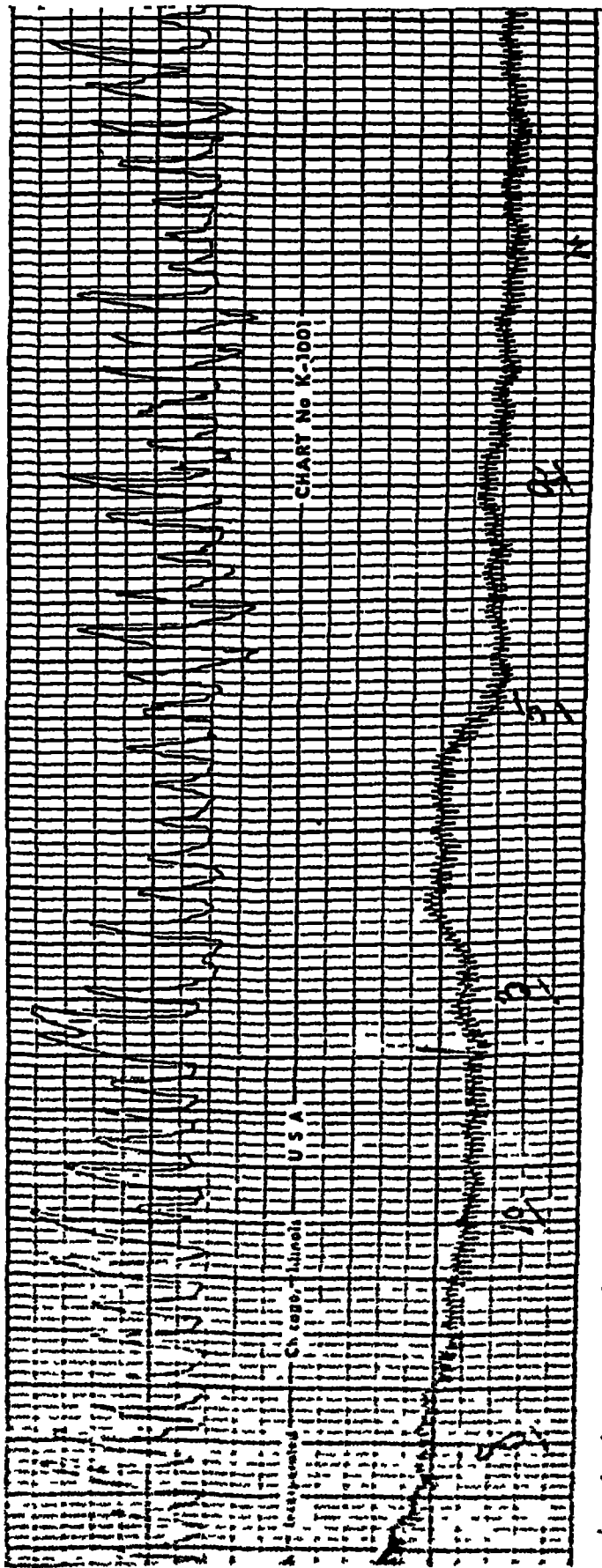


Fig. 3. A portion of the number test on Highland Nevins. The number he had selected was 3. Note the elevation and fall in blood pressure after beam; questioned on this number and also the suppression of the respirations at this point.

stated that he admitted the shooting occurred on November 21, 1942 and then he had buried her on November 28. Officers went to the Nevins home, and although there was a heavy fall of snow on the ground the grave was located, and on digging down about a foot and a half they found the body of Mrs. Pitts. An autopsy disclosed that she had been shot with a .22 caliber bullet squarely between the eyes. The bullet had fractured the base of the skull and coursed downward toward the back of the neck.

Nevins was arrested but insisted that he did not shoot Mrs. Pitts. His story was that when he went up to the trailer at about 7 p.m. on November 21 he found her dead and didn't know whether someone else had shot her or whether she had committed suicide. He told in great detail how he had picked the body up and kissed it but had finally left it as he had found it. The following day he had returned and cleaned up the blood and laid the body out carefully on the floor. He came nearly every day until the evening of November 28 when he placed the body in the back seat of his car and took it home. He borrowed a shovel and dug a hole in the back yard, and when some neighbors inquired what was going on he replied he was digging a new privy vault. The body was placed in the hole and covered up.

The bullet which had killed Mrs. Pitts had been fired from a rifle owned by Nevins. He said that the rifle had been loaned her some time ago for protection as she lived in a lonely place. In the meantime he had taken the rifle home.

When run on the lie detector, the card test was first employed. Nevins showed a definite reaction to card number 3 which was the one he had selected. When questioned on the shooting of Mrs. Pitts, Nevins showed definite reactions to the questions

5 Did you shoot Ellen?

7 Did you have an argument with Ellen?

9 Have you lied to any of these questions?

A repetition of the test disclosed identical reactions. Following the polygraph examination, Nevins signed a confession that he had intentionally shot and killed the victim.

The facts were that Nevins had become jealous because Mrs. Pitts was running around with some other men. On November 21 Nevins went up to the trailer in the morning and picked her up. They had been together practically all day drinking beer in several different taverns. About 6 o'clock in the evening they went back to the trailer and the argument started about Mrs. Pitts' relations with other men and during this Nevins picked up the rifle and shot her while she was sitting on a box. From that point on, the story was substantially as related by Nevins prior to his confession.

This illustrates a rather common type of case. Nevins was distinctly the bully type, often threatened and abused his wife, was a heavy drinker, had been arrested for assault and battery but had never been involved in serious trouble. Had Nevins stuck to his original story it is exceedingly doubtful if he could have been convicted of the murder charge. Picking his chosen number on the card test had definite value. Following the examination Nevins was told that he was not telling the truth with reference to the 3 pertinent questions and it was pointed out to him on the tracings just what his reactions were. As happens frequently in cases of this type, his armor of defense crumpled and the confession followed.

Part A

TEST 1
HARLAND REYNOLDS
9-6105 12-14-42

Associated - Research - Incorporated Chicago - Illinois U S A

Q DO YOU HAVE 3 D WERE YOU JEALOUS OF 4 D DID YOU SNOVE 5 D DID YOU SHOOT ELLEN
A YES A NO A YES A NO A YES A NO

Q DO YOU EAT THIS NOON
A YES

Q DO YOU HAVE AN ARGUMENT WITH ELLEN ON NOV 21ST
A YES

Q DID YOU GO TO SCHOOL IN MICH
A YES

Q HAVE YOU LIED ANSWERING ANY OF MY QUESTIONS
A NO

Part B

Q DO YOU EAT THIS NOON
A YES

Q DID YOU HAVE AN ARGUMENT WITH ELLEN ON NOV 21ST
A YES

Q DID YOU GO TO SCHOOL IN MICH
A YES

Q HAVE YOU LIED ANSWERING ANY OF MY QUESTIONS
A NO

Q DO YOU SNOVE
A YES

Q DID YOU SHOOT ELLEN
A YES

Q WERE YOU JEALOUS OF
A YES

Q DO YOU HAVE
A YES

Q DO YOU EAT THIS NOON
A YES

Q DID YOU HAVE AN ARGUMENT WITH ELLEN ON NOV 21ST
A YES

Q DID YOU GO TO SCHOOL IN MICH
A YES

Q HAVE YOU LIED ANSWERING ANY OF MY QUESTIONS
A NO

5 Per document test on Harland Reynolds Note the definite reactions to questions 5, 7 and 9.

SUMMARY AND CONCLUSIONS

During the last eight years the Michigan State Police have made use of the lie detector in the investigation of 905 criminal cases. Fifteen hundred fifty-one persons have been tested with the instrument and of these 563 showed guilty knowledge of the crime under investigation. Following the test, 308 of these persons made admissions of guilt, 803 persons were cleared and no analysis was possible in 75 cases.

The lie detector used by this department is an instrument which records changes in blood pressure and respirations. As with all apparatus which records physiological reactions, the interpretation of the findings is the crux of the procedure.

We recognize that the lie detector test has certain pitfalls, and every precaution must be taken to guard against errors of interpretation. As far as it is possible to check the results, the device and technic have shown a high degree of accuracy. By means of this technic many persons have been induced to confess to the commission of serious crimes, who without the use of the lie detector, undoubtedly would never have been convicted. Likewise, in several instances persons against whom there was strong evidence of guilt have been cleared by the lie detector and their innocence later substantiated. In the opinion of the Michigan State Police, interrogation by means of the lie detector provides a scientific, humane and highly accurate adjunct to criminal investigation.

LEGAL-MEDICAL ASPECTS OF BLOOD TESTS TO DETERMINE INTOXICATION *

By MASON LADD † and ROBERT B GIBSON, ‡ *Iowa City, Iowa*

THE development and use of chemical tests to determine intoxication has been due in a large measure to the activity of the National Safety Council in its effort to control the vast number of traffic accidents which have been caused by drunken driving. Its interest in national safety has resulted in active work to seek out the causes of injury and death arising from motor vehicle accidents with a view of preventing them. In this age in which practically all members of American society operate motor vehicles it is inevitable that many accidents occur both on open highways, which present opportunities for high speed, and in congested areas, where ordinary driving of a motor vehicle requires skill and alertness of mind. It is the interest in public safety that has caused legislatures to enact statutes making the operation of a motor vehicle while intoxicated a crime. Fear of criminal prosecution is counted upon to control or at least to retard drivers from operating motor vehicles when under the influence of intoxication. Fear of the law in the abstract, however, is but slight if the prosecution under the law cannot result in conviction of those guilty of the offense. Every public prosecutor knows the difficulty in trying this kind of case. The defense interposed always has some plausible excuse, either that the accused had liquor on his breath but had not imbibed excessively, or that the stupor and other objective manifestations of drunkenness were produced by shock, by the injury which the accused himself may have suffered, or by some other cause than intoxication. In some instances it is undoubtedly true that these are the causes and that an innocent person, because of his conduct and appearance, is facing prosecution. To determine the truth or falsity of the defense and the correctness of the charge against the accused, chemical fluid tests can solve the issue accurately in many cases. These tests should not stand in place of the usual evidence introduced as proof, but should be used as supplementary evidence. When the alcoholic content in body fluid is sufficiently high, this scientific test is unquestionably the most reliable method of determining intoxication. When properly used in the trial it should be most effective in bringing about just results.

The best method to control drunken driving is public education, making motorists and society aware of the danger to others and to themselves. However, to the extent that fear of the criminal law and of police officers helps to deter or control behavior in society, success in the prevention of criminal offenses is so important that simply enacting the crime of

law upon the statute books. Therefore, a more effective means of establishing guilt of the accused in criminal cases involving intoxication would substantially aid in keeping the drunken driver off the highway. From the standpoint of the individual case on trial, whether a criminal prosecution or a civil suit for damages, this recent method of determining intoxication should be of great assistance to courts and triers of fact in obtaining a just decision. Realizing the importance of the chemical test to determine intoxication, the National Safety Council has published and collected the works of numerous scientists and legal scholars pertaining to the subject and has used this material to inform law enforcing agencies of the possibilities for using this test and to inform the public of its value. Through this Council, in cooperation with state safety councils, legislative enactments permitting the use of these tests in evidence have been obtained. Today there are modern statutes on the subject in Indiana, New York, Maine and Oregon.¹ In many states the courts have admitted these tests without the aid of statutes and although legislation gives legal sanction to this procedure, similar results can be accomplished through the decisions of forward-looking courts. It is proposed in the following discussion to present concisely the significant medical and legal problems involved in the use of the body fluid test to determine intoxication.²

The determination of the alcohol content of the blood for evidence of intoxication is not a recent procedure. Grehant in the nineties studied the blood alcohol level after fatal doses of alcohol administered to dogs, later (with Nicloux), using more delicate analytical tests, he confirmed his earlier work. Nicloux suggested the medico-legal application and urged the adoption of such procedure. Widmark's correlation of blood alcohol levels and intoxication in man was undertaken previous to and during World War I. The test became mandatory in 1934 in Sweden largely through his influence. Blood alcohol tests for intoxication were ordered in Germany (1936) after a preliminary period of actual trial, and in Denmark, France and Switzerland. Blood and urine alcohol tests for intoxication are recognized now in our lower courts, and blood and urine alcohol levels defining intoxication are in the statutes in some states.

The amount of alcohol in the blood is the best measure of intoxication, as shown by many reports and data on many thousands of cases in Europe and in this country.³ Urine alcohol values commonly exceed those of the blood (1.35 : 1) and individual variations are found. The urine test is sig-

¹ Burns, *Indiana Statutes Annotated* (1940) Tit. 47 § 2003, *McKinney's Consolidated Laws of New York* (1942) § 70 (5), *Laws of Maine* (1939) Ch. 273, *Oregon Laws* (1941) Ch. 430.

² In 1939 these writers of the present article wrote a more extensive paper considering this subject in greater detail. See Ladd and Gibson, *The Medico-Legal Aspects of the Blood Test to Determine Intoxication*, 24 *Iowa Law Review* 191-267. The present article includes discussion and references showing later developments.

³ See note 2 *supra*. Later reports to the same effect include Jettler, W. W., *The Chemical and Clinical Diagnosis of Acute Alcoholism*, *New England Jr Med* 1939, vol. 1019, and BRYAN, D. F., 145 drunken drivers—a blood and urine alcohol study, *Jr Lab and Clin Med.* 1940 Vol. 823.

nificant when the critical alcohol content indicative of intoxication is set at a higher level.

Figures for blood (or urine) alcohol content are to be presented as only a part of the proof of intoxication. Dependence on the blood alcohol test alone or too much emphasis on its conclusiveness will weaken the prosecution. For example, a physician may make a diagnosis of and estimate the severity of a diabetic or uremic condition by quantitative blood tests for glucose or urea alone, but the patient's history, physical examination and other laboratory reports usually come first and the quantitative analyses on the blood complete the picture. In endeavoring to establish (or rule out) a state of alcoholic intoxication, all of the information to this effect should be presented.

The signs and symptoms of intoxication then are important whether noted by the physician or others. The effect of alcohol is principally on the nervous system. It produces mental disturbance, neuromuscular incoordination, and in large amounts narcosis. Deaths from acute alcoholic poisoning are not uncommon. There will be an odor of alcohol on the breath or in the vomitus, a furred tongue, salivation and intermittent hiccup. Irregularity of behavior is outstanding, i.e., insolence, use of abusive language, loquacity, excitement, sullenness, disorder of dress. There is loss or confusion of memory especially concerning recent events and impaired appreciation of time. Speech is hesitant and thick and articulation is impaired. Abnormality of the pupils (various forms), suffusion of the conjunctiva and convergent squint (esophoria) may be noted. The face is flushed. There is tremor. Errors of neuromuscular coordination and of orientation occur as shown by the manner of walking, turning sharply, sitting down and getting up, picking up small articles from the floor, and swaying or falling when standing with the feet together and closing the eyes (Romberg sign). The above symptoms will vary with individuals and in proportion to the quantity of alcohol ingested. With large amounts taken, the individual passes into the paralytic stage. The respiration is slow and stertorous, the pulse weak, the skin cold and cyanotic, the pupils dilated, the reflexes are lost and the body temperature below normal. If large amounts are taken on an empty stomach, the paralytic symptoms may be manifested in a short time.

The application of legal technics involved in the introduction of the blood and urine alcohol test to establish intoxication will be described. However, some discussion of blood alcohol levels in relation to intoxication seems desirable at this point.

A blood alcohol figure of 150 milligrams per 100 cubic centimeters of blood (or 0.150 per cent by weight) ⁴ is considered indicative of intoxication because at that level practically everyone shows sufficient deterioration of

⁴ Reports on body fluid analyses generally are expressed in clinical reports as milligrams per 100 cubic centimeters or simply mg per cent. In states where the blood or urine alcohol content defining intoxication is included in the statutes, it would be best to use such terminology in the trials (usually per cent by weight). Milligrams per cubic centimeter (mg per c.c.) are often used. Breath alcohol is in direct relation to that of the blood and is expressed in terms of blood alcohol concentration as above.

judgment and interference with neuromuscular coordination to be a menace to himself and to others. A few individuals are intoxicated at levels not much over 50 mg per cent. Others hardly appear intoxicated at 150 mg per cent or more, though behavior and clinical tests will demonstrate that they are affected.

The following correlation (from the literature and our own experience) of blood and urine alcohol levels, quantity of liquor consumed, and stage of intoxication has been useful in court. Stages 3, 4 and 5 necessarily overlap.

- 1 Normal, blood and urine alcohol 5 to 15 mg per cent
- 2 Social stage, blood up to 50 mg, urine 10 to 60 mg per cent, two glasses or bottles of beer, or one highball or cocktail (two when taken with chips, crackers, etc.) Effects are slight, feeling of bodily warmth and well being, mild euphoria, behavior tests normal
- 3 Preintoxication to intoxication stage (stimulation stage), blood 50 to 150 mg, urine 60 to 200 mg per cent, two to eight bottles of beer or two to four highballs. Release of social inhibitions, emotional instability, slowed response to stimuli and neuromuscular incoordination. Some individuals are easily recognized as intoxicated at 90 mg, others seemingly are not much affected at 150 mg per cent in the blood, but judgment is impaired and their control required for quick responses is impaired.
- 4 Intoxication stage (confused stage), blood 150 to 300 mg, urine 200 to 400 mg per cent, one half to one pint of whiskey over a short drinking period. Symptoms and behavior typical for intoxication.
- 5 Stuporous stage, blood 300 to 400 mg, urine 375 to 500 mg per cent, one pint or more of whiskey. Stupor, responds only to strong stimuli.
- 6 Paralytic stage, coma or narcosis, blood 400 to 600 mg per cent. Cannot be aroused, depressed reflexes, subnormal temperature, stertorous breathing, possible death.

Failure to take certain precautions in the obtaining and subsequent handling of blood and urine specimens may lead to exclusion of the fluid test as evidence. If possible, consent of the person in question for the taking of blood or urine specimens for the alcohol test should be obtained in the presence of witnesses. Blood should be drawn or urine collected as soon as possible, as alcohol is oxidized in the body and the blood level decreases about 20 mg per cent an hour.^a The blood should be taken in the presence of witnesses by a police surgeon or a physician or by a nurse or laboratory technician (if not prohibited by statute), urine samples may be collected by a police officer—an advantage in employing urine for the test. The syringe and needle should be dry or steam sterilized, only bichloride solution or cake soap and water (never alcohol) should be used in disinfecting the skin. The

^a In New York the specimen must be taken within two hours of the time of arrest.

container into which the specimen is discharged should be sealed and labeled with the name of the donor, the date and hour obtained, the physician's name, and the names or initials of the witnesses⁶. The physician should make and record the usual neurological (and behavior) tests and form an opinion as to intoxication. He should avoid establishing a physician-patient relation as this may lead to the exclusion of his testimony and of the evidence of the blood alcohol test in the trial.

Continuity of possession of the blood or urine specimen until introduced as an exhibit in the trial must be assured. If convenient, the physician or other person who took the specimen from the prisoner may place it in the hands of the laboratory director or of the analyst, or it may be brought to the laboratory by a police officer or deputy who received it from the hands of the physician. A notation of the date, and from whom and by whom it was received should be made. Specimens may be mailed, preferably special delivery or registered, however, specimens received in the course of ordinary delivery of the United States mail are accepted by the courts. A part of the blood or urine necessarily will be used up in the analysis, the container with the remainder of the specimen therein should be sealed and kept under lock and key by the laboratory director or the analyst until delivered to the county attorney or on his written order or until the case has been disposed of legally.

A great responsibility is put upon the chemist or technician who actually determines the alcohol content of the specimen. His efficiency should have been proved by actual determinations of known amounts of alcohol added to blood or urine and by his ability to check with the figures obtained by experienced analysts on specimens brought to the laboratory. The analytical method should be one recognized as reliable by biochemists and clinical pathologists and the detailed procedure available in a standard text or journal. When the analysis is done by a technician, it should be at the direction and under the supervision of the laboratory director, not only to insure against technical error but in order that either person may testify as to the alcohol content found. The test should be made in duplicate and the results should check. If the blood specimen is not sufficient in quantity for duplicate determination (including the distillation), the analysis is, nevertheless, admissible and is valuable as proof when in accord with other evidence of intoxication. Analytical notes should be kept and filed. Analyses should be made with reasonable promptness. Results may be telegraphed, telephoned or police-radioed to the police station, sheriff or county attorney if requested. A written report should follow for their records.

In presenting witnesses and giving testimony, a chronological order of obtaining the specimen and carrying the test through to its conclusion is best followed. Ordinarily, the events involved in the litigation will have been presented in the trial by other witnesses. Some of these, after testifying

⁶ It may be advisable to obtain a duplicate specimen of the blood when drawing it and to seal and retain it for use should the defense request a specimen for a check test.

as to other matters they have perceived,⁷ will give testimony as to their connection with the blood test. The technical evidence pertaining to the test constitutes a distinct and somewhat separate part of the total testimony in the case. The first witnesses to testify in this part should be those participating in taking the specimen. The physician who has taken the blood sample should testify as to obtaining the consent of the party, if required, the time of drawing the specimen, and the procedure and the precautions taken to avoid the introducing of foreign material which might influence the subsequent analysis. He should then identify the container (with the residue of the specimen) offered as an exhibit by the prosecution. He should testify when and to whom the specimen was delivered and mailed. This witness should not be questioned extensively in direct examination, if at all, on the consequences of the test. His function is to show that he has a clean, safe blood specimen and that it was transmitted properly for chemical analysis. He may not be a real expert upon the analysis of the blood (or urine) nor familiar with the literature on the results of the blood alcohol test and could be confused easily by cross examination with respect to the test. If gone into with him on direct examination, he is exposed to all of the fire of cross examination and may ruin a case before the expert on the subject takes the stand. If an intern, a nurse or technician (or on occasion a police officer for urine) has drawn the specimen, such witness should be put on the stand and should testify as above.

The analyst very commonly is the expert as well, though these two functions at times might be separated with different witnesses giving the testimony. In either event testimony pertaining to the analysis should be given first and with meticulous care. The analyst should give qualifying testimony as to his training and experience, especially with reference to the determination of the alcohol content of blood and urine. He should identify the container and contents (exhibit—) and state from whom and the time when he received it. He should name the method of analysis,⁸ outline briefly the procedure and precautions to assure accuracy, the quantity of alcohol found and the subsequent disposal of the container and remaining specimen.

⁷ The Iowa State Highway Patrol and the local police have shown excellent judgment in their estimation of acute alcoholism. In a period from February 1, 1939 to July 1, 1941, 336 tests on blood alcohols were made at the University Hospital. There were 4.4 per cent of these containing less than 50 mg. per cent of alcohol, and the specimens were sent in for the establishment of innocence and usually on the individuals' own initiative. The remaining 95.6 per cent were distributed as follows: 50-99 mg., 1.5 per cent, 100-149 mg., 6.2 per cent, 150-199 mg., 19.3 per cent, 200-249 mg., 29.2 per cent, 250-299 mg., 25.0 per cent, 300-349 mg., 9.2 per cent, 350-399 mg., 3.2 per cent, and 400-449 mg., 1.2 per cent.

⁸ See Ladd and Gibson *op cit supra* note 2, pp 210-212 for a brief description of the analytical methods for blood and urine alcohol. Also Levine, H., and Bodansky, M. Determination of alcohol in tissue and body fluids: summary of practical procedures for the pathological laboratory, *Am Jr Clin Path*, Tech Suppl, 1939, iii, 159, A simple and accurate method for the determination of alcohol in body fluid, *Am Jr Clin Path*, 1940, iv, 103, and Johnston, G. W., and Gibson, R. B. A distilling apparatus and a procedure for the determination of alcohol in blood and urine, *Jr Lab and Clin Med*, 1940, xxvi, 399. The accuracy of the breath test as carried out has recently been questioned by Haggard, H. W., Greenberg, L. A., Miller, D. P., and Carrol, R. P. The alcohol of the lung air as an index of alcohol in the blood, *Jr Lab and Clin Med*, 1941, xxvii, 1527.

The effect of the alcohol content of the blood should be the last testimony offered in the blood test evidence. This witness should qualify truly as an expert if the testimony is to carry weight with the triers of fact. Some statutes provide that a given percentage of alcohol in the blood (or urine) creates *prima facie* evidence of intoxication. In other states this effect must come through the opinion testimony of the expert, and in all cases this is desirable to make the testimony effective. Experience has shown that it is upon this problem that the greatest amount of cross examination is developed. The expert must be fully qualified, well read in the literature of the subject, and it is desirable that he should have had first hand experience in making analyses and comparisons of blood alcohol content in relation to intoxication. He may be a clinical pathologist, a physician who has made a special study, a pharmacologist, biochemist or chemist who has the foregoing qualifications. The validity of the test is recognized and its application sufficiently well known that the direct examination may be brief. After being duly qualified he should be questioned further as follows:

Q—From your study of the literature and your own observation and experience, are you able to correlate the amount of alcohol or alcoholic beverage consumed with a resulting blood alcohol level? ⁹

Q—Would you express your opinion as to how much beer (wine, or whiskey) an individual of average weight must drink over a period of one to two hours to bring the blood (or urine) alcohol to — mg of alcohol per 100 cc? ¹⁰

Q—Is there a recognized correlation between blood (or urine) alcohol levels and intoxication from alcohol? ¹⁰

Q—From your own study and experience would you say that an individual with a blood (or urine) content of alcohol of — mg per 100 cc of blood (or urine) was intoxicated? ¹¹

Q—Would you consider an individual with a blood (or urine) content of alcohol of — mg per cent to have been intoxicated at a time — hours previous to the time the specimen was obtained? ¹¹

Should the prosecutor desire to present to the jury more information regarding the test and its reliability, the following questions may be asked the witness prior to those suggested above. Like information will almost certainly be sought in the cross examination ¹²

⁹ Roughly 1 cc of alcohol per kilo (22 lbs) produces a blood alcohol level of about 100 mg per cent, 2 cc nearly 200 mg per cent, etc. Two cc of whiskey are equivalent to one cc of alcohol. One bottle (12 oz) of beer is about equal in alcohol content to one oz of whiskey.

¹⁰ Ladd and Gibson, *op cit supra* note 2, pp 262-267

¹¹ The time is the period between finding the person in question in apparent intoxication (or the time of an accident or other event) and the taking of the specimen. As blood alcohol is reduced through destruction in the body 15 to 20 mg per hour, such an estimate is feasible if the individual has taken no more liquor during the period.

¹² An excellent review of the metabolism and pharmacology of alcohol may be found in Sollman, T. A manual of pharmacology, 6th Edition, 1942, W B Saunders and Co, Philadelphia and London.

Q—Is alcohol normally present in the body (blood or urine) and in what quantity? Are there other substances in the blood or urine which will disclose similar results to this test? What happens to alcohol after it is taken into the body? How much is excreted in the breath and urine? How much alcohol in drops per ounce is — mg per cent? How does alcohol produce intoxication? What is the effect of food taken with intoxicating beverages? Are there not individuals who can have a blood alcohol level above 150 mg per cent who are not intoxicated? What is tolerance to alcohol?¹³ How do you calculate the amount of alcohol in the blood from the amount ingested? What other methods are used for the test other than the one employed? Is not the spinal fluid test better than the blood test? What is the National Safety Council? What is the basis for the 150 mg blood alcohol level as indicative of intoxication? The witness also should be familiar with such controversial literature as may be brought up in the cross examination

Thus far the methods in taking fluid tests to determine intoxication, their reliability as evidence, and the technics for proper presentation in court have been considered, but there are many questions purely legal in character which are all important to lawyers and of interest to the medical profession. To those not familiar with the legal issues it is somewhat of a mystery why the test should not be given to all persons having the appearance of intoxication when the question of their intoxication is involved in possible criminal behavior. The results of the test would serve to protect the innocent as well as to convict the guilty. It would seem that for good law enforcement and in the interest of public safety there should not be legal obstacles to prevent free use of the test. Indeed, to protect the unconscious person who is not intoxicated but appears to be, his best interests would be served by having the test taken without his consent. Most of the problems have arisen, however, as to the fact of consent, and at the present, at least, most courts seem to require that a person must consent to the fluid test as a prerequisite to its use in evidence. This requirement, in turn, raises the question of what constitutes consent by one charged with drunkenness. These problems will be considered separately. The first issue of the acceptance of the test in evidence as scientific proof of intoxication now may be safely regarded as settled, as in the courts of some 32 states fluid test evidence has been admitted as proof of intoxication. This accords with the position taken both by the National Safety Council and the American Medical Association.¹⁴

¹³ The question of tolerance required further investigation. At present it is taken care of by emphasis on the presentation of definite evidence of intoxication in addition to that of the blood test when the blood alcohol level is between 50 and 150 mg per cent. Above 150 mg the individual is considered drunk irrespective of idiosyncrasy or tolerance. A compensation for normal muscle-sense incoordination may be achieved by slowing the movements and using visual sense aid in controlling these. Newman and others have shown that the effects of alcohol are much more pronounced earlier when the blood alcohol content is maintained at a level for some hours. There seems to be a definite amelioration of the symptoms later. Newman, H., and Abrahamson, M. Relation of alcohol concentration to intoxication, *Proc Soc Exper Biol and Med*, 1941, LVIII, 509.

¹⁴ The Committee to Study Problems of Motor Vehicle Accidents of the A.M.A., Jr. Am. Med. Assoc., 1942, CLIX, 653, reiterates its former recommendation that the percentage of

The use of body fluid to determine intoxication at the outset faces two constitutional problems. In the Federal Constitution and in the Constitutions of all states except Iowa and New Jersey there is a provision against compulsory self-incrimination. The Fifth Amendment of the Federal Constitution is representative of these sections and provides that in any criminal case no person shall be compelled to be a witness against himself. In Iowa there is a statute to the same effect. In every case that has come before the courts in which the body fluid test has been taken without consent of the accused the defense has sought to exclude the evidence on the ground that it violates the privilege against self-incrimination. If this position is sustained by the Supreme Court of the various states, it means that use of the body fluid test cannot be made except when consent is given. Obviously the accused who knows he is intoxicated is not likely to give his consent, and the benefit of this type of evidence is lost in the cases in which it is most needed. In the cases in which the prosecution claims that the accused did consent, there will always be this question of fact to be determined as a condition precedent to the admission of this type of evidence. According to the more sound view of interpretation of the privilege against self-incrimination, it has no relationship to this kind of a problem. In the historical development of the privilege it was only used to prevent compelling an accused person to give incriminating testimony, that is, verbal or written testimony against himself.¹⁵

In numerous instances compulsory disclosures not verbally communicated and yet very damaging in their effect have been admitted in evidence against the defense that they were self-incriminating.¹⁶ The forcible taking of shoes from the accused for a comparison with tracks made at the scene of the crime is admissible.¹⁷ Except in Georgia¹⁸ it is generally held that the accused may be forced to place his foot or shoe into the disputed print, without violation of the privilege.¹⁹ Results of a physical examination of sexual organs of the accused made forcibly by a physician to determine pregnancy or disease are received in evidence in face of the privilege,²⁰ although alcohol in the blood is a reliable index of the degree of intoxication, especially when considered along with the external symptoms of intoxication.

1 Below 0.05 per cent alcohol in the blood no influence by alcohol within the meaning of the law.

2 Between 0.05 and 0.15 per cent, a liberal wide zone, alcoholic influence usually is present, but courts of law are advised to consider the behavior of the individual and circumstances leading to the arrest in making their decision.

3 0.15 per cent definite evidence of "under the influence," since every individual with this concentration would have lost to a measurable extent some of that clearness of intellect and control of himself that he would normally possess.

¹⁵ 8 Wigmore 3d ed §§ 2250-2252, Ladd and Gibson, *op cit supra* note 2, pp 225-232

¹⁶ Inbau, Self-Incrimination—What an Accused Person May Be Compelled to Do (1937)

28 J Crim L 261, Ladd and Gibson, *op cit supra* note 2, pp 232-241

¹⁷ *Biggs v State*, 201 Ind 200, 167 N E 129 (1929) and extensive note in 64 A L R 1085

¹⁸ *Day v State*, 63 Ga 668 (1879), *Elden v State*, 143 Ga 363, 85 S E 97 (1915)

¹⁹ Note 2, *supra*

²⁰ *Villafior v Summers*, 41 Phil 1s 62 (1920). See also *State v Eccles*, 205 N C 825, 172 SE 415 (1935). Contra *People v McCoy*, 45 How Prac (NY) 216 (1873). But in *People v Sallow*, 100 Misc 447, 450, 165 N Y Sup 915, 921, 36 N Y Crim 27, 37 the court said "The ruling in the case of *People v McCoy* in so far as it held that evidence by a

one state in an earlier case held that taking a blood test to determine disease could not be made under compulsion²¹ This case is out of harmony with the better view today The theory for admissibility is pointed out in the case of *State v Graham* in which the court stated "Confessions which are not voluntary but are made either under fear of punishment if they are not made, or in the hope of escaping punishment if they are made, are not received as evidence, because experience shows that they are liable to be influenced by those motives, and cannot be relied on as guides to the truth But this objection will not apply to evidence of the sort before us No fears or hopes of the prisoner could produce the resemblance of his track to that found in the corn field"²² In the Philippine case of *Villafior v Summers*, the court states "No accused person should be afraid to use any method which will tend to establish the truth No evidence of physical facts can for any substantial reason be held to be detrimental to the accused except in so far as truth is to be avoided in order to acquit a guilty person"²³ Not infrequently courts require the accused to change his wearing apparel and to don an article worn by the one who committed the crime to aid in identification, although the process is objected to under the self-incrimination doctrine²⁴ *Shaffer v the United States* is an interesting case in which evidence of the photograph of the accused, taken immediately after the crime, without his consent, was held admissible for the use of a witness to identify him, he having grown a full beard²⁵ The dicta, in the case of *Johnson v Commonwealth*, approved requiring the accused to speak for the purpose of identifying his voice, and, although without the Supreme Court decisions in point, the practice is commonly used²⁶ Physical examinations to determine the sanity of an accused person are not contrary to the privilege²⁷ Some courts have held that handwriting demanded by an officer after arrest, whether objected to or not, is admissible evidence and not within the privilege against self-incrimination²⁸ Justice Holmes, in the case of *Holt v State*, summarized the correct principle well, stating "But the prohibition of compelling a man in a criminal court to be a witness against himself is a prohibition of the use of physical or moral compulsion to exhort communication from him, not an exclusion of his body as evidence when it may be material

When he is exhibited, whether voluntarily or by order, and even if the order goes too far, the evidence if material is competent"²⁹

compulsory physical examination of the defendant was not admissible in evidence must be overruled by the authorities cited"

²¹ *State v Height*, 117 Ia. 650, 91 NW 935 (1902) See criticism Ladd and Gibson, *op cit supra* note 2, pp 215-225

²² 74 N C 646, 647 (1876)

²³ 41 Phil Is 62, 69 (1920)

²⁴ *Holt v United States*, 218 US 245, 252 (1910), *State v Aschoa*, 49 Nev 194, 242 Pac 582 (1926)

²⁵ 196 U S 639 (1904)

²⁶ 115 Pa St R 369, 9 Atl 78 (1887)

²⁷ *Commonwealth v Mulder*, 289 Mass 441, 194 NE 463 (1935), *Jessner v State*, 202 Wis 184, 231 NW 634 (1930)

²⁸ *Sprouse v Commonwealth*, 81 Va 374 (1886), *State v Owens*, 167 Wash 283, 9 Pac (2d) 90 (1932)

²⁹ *Holt v United States*, 218 US 245 (1910)

There has been but one court to date which has refused to admit the blood test to determine intoxication obtained without the consent of the accused because it was a denial of the privilege against self-incrimination. A number of courts have talked about it in their comments but have decided the case upon other grounds. In the Texas case of *Apodaca v State* the court definitely held that taking the test under such circumstances was a denial of the constitutional privilege.³⁰ This opinion is reactionary from many angles. It even went so far as to deny officers the right to compel the accused to walk and make sudden turns, to hold out his hand, and to give the usual tests employed to determine intoxication from objective observations. This Texas case does not discuss the theory of the law nor its history. If carried to its logical conclusion it would no longer permit officers to compel a person under arrest to submit to fingerprinting³¹ or to the taking of a photograph. The Texas, Cincinnati and Washington Law Reviews, in commenting upon the case, reached the conclusion that it was wrong and that it followed the old rule of compulsion alone.³² In the three cases in which the matter has been discussed by the Iowa Supreme Court a more hopeful attitude is indicated.³³ The Court has found some other means of deciding the issue than upon the point of the necessity of consent. In the most recent case of *State v Benson* Chief Justice Miller wrote an illuminating opinion holding that where the accused refused to permit the test to be taken when requested by the police officer, the prosecution could comment upon it and the jury could consider it in the nature of an admission.³⁴ This court applied the rule that the prosecution may comment about the accused's failure to testify to the situation in which the accused had refused to consent to a blood test. The Ohio case of *State v Gatton* had the problem squarely before it, and the court held that consent was not necessary for the taking of a body fluid test and that compulsion was not a denial of the privilege against self-incrimination.³⁵ In most of the cases that have come before Appellate Courts over the country there has been sufficient evidence of consent on the part of the accused to make it unnecessary for the court to decide the issue of whether the constitutional provision applied.³⁶ The American Law Institute, in its Model Code of Evidence Rule 205, definitely takes the position that it is not a denial of the privilege to compel an accused person to submit his body to examination for the purpose of discovering or recording his corporal features and other identifying characteristics or his physical or mental condition or to furnish

³⁰ 140 Tex Cr R 593, 146 S W (2d) 381 (1940)

³¹ The legality of taking Bertillon measurements and fingerprints is discussed in *United States v Kelly*, 55 Fed (2d) 67, 83 A L R 122 (C C A 2d, 1932) and note

³² 19 Tex L Rev 463 (1941), 15 Cincinnati L Rev 344 (1941), 26 Wash L Rev 435 (1941)

³³ *State v Morkrid*, 286 N W 412 (Iowa 1939), *State v Weltha*, 228 Ia 519, 292 N W 148 (1940), *State v Benson*, 230 Ia 1168, 300 N W 275 (1941). The last case written by Chief Justice Miller takes a much more enlightened position than the earlier cases

³⁴ Id

³⁵ 60 Ohio App 192, 20 N E (2d) 265 (1937)

³⁶ *State v Cash*, 219 N C 818, 15 S E (2d) 277 (1941), *Commonwealth v Capalbo*, 308 Mass 376, 32 N E (2d) 225 (1941)

or to permit the taking of samples of body fluids or substances for analysis^{36a} This forward-looking position taken by the American Law Institute is bound to have a significant influence in molding the law of the future A great amount of literature and many decisions of the Courts exist dealing with the subject of the privilege against self-incrimination³⁷ It is a significant phase of constitutional law and the law of evidence The original or orthodox view and that taken by modern thinkers upon the subject are in accord that the privilege does not deal with anything other than testimonial communication Some state courts have enlarged upon this beyond any intended constitutional limitations without thought of the objective sought to be accomplished by the privilege Logically or historically the privilege should not be extended to the body fluid cases any more than to the fingerprint cases or other objective manifestations which could not be altered as a result of their compulsory taking Verbal testimony might be subject to change with the influence of compulsion upon the accused, but fingerprints or body fluids would be the same whether taken with or without consent

Another problem that has caused some courts difficulty upon the constitutional issue is whether the taking without consent of a body fluid from a person accused of crime is an unlawful search and seizure Here again the few courts that have taken the position establishing the illegality of such procedure have really built into this constitutional inhibition something of their own making unsupported historically or upon any logical basis³⁸ This application has but such slight recognition today that it is unnecessary here to consider it at length The Fourth Amendment of the Federal Constitution and similar provisions in state constitutions relate to unlawful search and seizure of a person's home or of the person for chattels or papers which he might possess The doctrine has no application to the physical examination of the person for purposes of identification and should not apply to the compulsory taking of body fluids for testing purposes

There is another doctrine involved which has not been very fully developed and which may give rise to some difficulty In one case relating to the taking of blood samples on the issue of paternity the court developed the thought that it was a denial of due process of law and an invasion of the right of privacy of the person This New Jersey case of *Bednarik v Bednarik* should have some consideration here because of its possible relationship to the blood test to determine intoxication³⁹ It was an action for divorce on the ground of adultery The plaintiff's husband made an application for an order to compel a blood test of him, his wife and his child to determine whether or not he was the father of the child A New Jersey statute au-

^{36a} See in this Symposium Series Morgan Suggested remedy for obstructions to expert testimony by rules of evidence, 2 Clinics (April 1943), Chicago Law Rev — (April 1943)

³⁷ Note 2, *supra*

³⁸ 8 Wigmore, *op cit*, *supra* note 15, §§ 2175-2183, Ladd and Gibson *op cit*, *supra* note 2, pp 215-218

³⁹ 18 N J Misc 633, 16 Atl (2d) 80 (1940)

thorized the use of blood grouping tests to determine paternity. It was held that to grant the petition would amount to an unconstitutional invasion of the right of personal privacy of the defendant and the child. The court commented as follows:

"To subject a person against his will to a blood test is an assault and battery, and clearly an invasion of his personal privacy. It involves the sticking of a surgical needle into his body. Perhaps the operation is harmless in the great majority of cases, although the risk of infection is always present. But if we admit such an encroachment upon the personal immunity of an individual where in principle can we stop? Suppose medical discovery in the future evolves a technique whereby the truth may infallibly be secured from a witness by trepanning his skull and testing the functions of the brain beneath. No one would contend that the witness could be forced against his will to undergo such a major operation at the imminent risk of his life, in order to secure evidence in a suit between private parties. How then can he be forced to undergo a less dangerous operation, and at what point shall the line be drawn? To my mind it is not the degree of risk to life, health or happiness which is the determinative factor, but the fact of the invasion of the constitutional right to privacy." ¹⁰

A comment in the *University of Pennsylvania Law Review* criticized the decision because it apparently regards the right of privacy as an absolute right although it has never been so considered.¹¹ In the *Bill of Rights Review* a very excellent discussion of the whole subject is presented and a view is taken contrary to the *Bednarik* case.¹² To make blood tests to determine paternity only a few drops of blood are needed for the comparative analysis. The court overemphasizes the seriousness of the risk involved in making such a test particularly when done by expert medical men. From the attitude expressed in the foregoing statement the court apparently assumes an inability upon the part of courts to use their good plain judgment and common sense in determining what might be a serious medical examination endangering health of the patient, and what might have but the most remote possibility of causing harm. The court ignores the many tests commonly required of persons now in carrying out the law in diverse situations. The opinion seems to overlook the fact that many states require a venereal disease test before parties are permitted to marry. Surely compulsory vaccination required of students in schools submits the person to a much greater danger than taking a sample of blood for analysis. The great number of tests now daily imposed by the army and the navy in the interests of the health of men in the service have not resulted in the widespread suffering which this opinion seems to assume would result from a compulsory blood test where it might

¹⁰ *Id.* p. 652

¹¹ 89 *Univ. Pa. L. Rev.* 518 (1941)

¹² 1 *Bill of Rights Rev.* 226 (1941)

produce scientific, reliable evidence. In workmen's compensation cases courts have generally recognized the principle that an injured employee cannot claim compensation when a slight operation would remove the disability.⁴³ In these cases the courts are required to determine the difference between a serious operation which might be of real danger to the employee and an operation which might be regarded as having slight possibilities of danger. It should not take much effort upon the part of a court to realize that taking a few drops of blood by expert medical men could not be regarded as impairing the health or life of an individual. It is believed fair comment to say that the *Bednarik* case has greatly overemphasized the danger involved in making a test and this overemphasis makes the argument that the test constitutes an invasion of privacy fallacious.

There is one very real difference between the taking of blood in cases involving paternity of a child and the taking of a body fluid specimen for evidence against one accused of a crime. In the latter situation the accused is under arrest, which enlarges upon the things which may be legally done to him. For example, it is unlawful for officers to search and seize things from the person of an ordinary citizen, but if he is lawfully arrested the right of search and seizure of things from his person exists as a matter of law. The blood test to determine intoxication will be largely used in criminal cases, perhaps mostly in drunken driving cases, and in practically every case in which the test is taken the accused has already been placed under arrest. There is a substantial difference, therefore, between these two classes of cases. However, it seems clear that the New Jersey decision was wrong even in the paternity issue. The court might well have concluded that, although the mother could have refused for herself and child to submit to the blood test, by doing so she would be compelled to forego the prosecution of her civil suit for divorce.⁴⁴ Where scientific evidence might accurately and honestly solve the issue in dispute, it is hardly in the public interest that some legal barrier prevents its use in cases in which the test would cause but slight inconvenience to the parties affected.

If the court should ultimately adopt the view, which it is hoped it will not, that it is necessary that there be consent on the part of the accused before a blood test is taken, the legal issue of what constitutes consent is presented. The first Supreme Court decision upon this subject is the Arizona case of *State v. Duguid* in which it was held that consent resulted from the accused's failure to resist and that he had thereby waived the privilege against self-incrimination.⁴⁵ Practically all cases dealing with this subject upon analogous situations have reached the same conclusion.⁴⁶ It might be claimed that

⁴³ *O'Brien v. Albrecht*, 206 Mich. 101, 172 N.W. 601 (1919), *Joliet Motor Co. v. Industrial Board*, 280 Ill. 148, 117 N.E. 423 (1917), Ladd and Gibson, *op cit supra* note 2 pp. 239-241. And see, in this Symposium Series, Ludlam, Plaintiff's Duty to Submit to Surgery to Minimize Defendant's Liability to Damages" (In press).

⁴⁴ This would be analogous to the treatment of the Workmen's Compensation cases. Note 29 *supra*.

⁴⁵ 50 Ariz. 276, 72 Pac. (2d) 435 (1937).

⁴⁶ Cases collected and discussed, Ladd and Gibson, *op cit supra* note 2, pp. 241-251.

if intoxicated, the party did not have the capacity to give his consent. This view has not been accepted, except in the case of complete intoxication so that the accused is not conscious of what he is doing. The consent issue would be material, however, in the case of an injury to the drunken driver causing him to be unconscious. In this situation it would seem that for the benefit of the innocent accused the law ought to create some sort of an implied consent if consent is to be demanded at all. A rational application of the consent doctrine might well be that consent would be deemed to exist in all cases in which there was not a definite refusal.

The character of legislation upon the subject is in part related to the constitutionality of taking a compulsory test. If the court should adopt the view that a compulsory body fluid test is a violation of any constitutional provision, statutes providing for a test under such circumstances would be unconstitutional. The statute in Oregon provides for taking the chemical test unless the arrested person objects to it.⁴⁷ It also provides that a refusal of the arrested person to submit to the test shall not be admissible evidence against him. This later provision is contrary to the decision of the Iowa court in the *Benson* case. The Oregon statute makes no provision for the weight of the test as evidence but leaves this to the opinion of the experts giving testimony. The Maine statute specifically provides that certain percentages of alcohol in the blood shall be prima facie evidence that the defendant was under the influence of intoxicating liquor within the meaning of the motor vehicle act.⁴⁸ It then provides that the failure of a person accused of this offense to have tests made shall not be admissible in evidence against him. There is nothing in this statute specifically requiring consent before officers might order the taking of a body fluid test. The New York statute has no express provision requiring consent of one under arrest before taking the test but made such evidence admissible if the test is taken within two hours of the time of arrest.⁴⁹ It contains no provision against the compulsory taking of the test and it would seem that it is inferentially authorized. The Indiana⁵⁰ statute and the New York statute are practically the same.⁵¹

In the Indiana, Maine and New York statutes it is provided that if the body fluid contains .05 of 1 per cent or less by weight of alcohol it is prima facie evidence that the defendant was not intoxicated, between .05 of 1 per cent and less than .015 of 1 per cent by weight of alcohol in the blood relevant evidence of intoxication exists but it is not to be given prima facie effect of intoxication. If there was .015 of 1 per cent or more by weight of alcohol in the blood, this may be admitted as prima facie evidence that the

⁴⁷ Oregon Laws (1941) Ch. 430

⁴⁸ Laws of Maine (1939) Ch. 273

⁴⁹ It may be desirable that new definitions of intoxication be established to fit the danger involved. The state of intoxication to constitute a public danger might differ substantially for one walking down the street from one driving a motor vehicle or piloting an airplane. For excellent discussion of this problem see, Hall, Drunkenness as a Criminal Offense, 1 Quarterly Journal of Studies on Alcohol 751 (1941).

⁵⁰ McKinney's Consolidated Laws of New York (1942) § 70 (5)

⁵¹ Burns Indiana Statutes Annotated (1940) Tit. 47 § 2003

defendant was in an intoxicated condition. These provisions are significant. They make it technically unnecessary for the expert witnesses to testify as to the consequences of alcohol in the blood. When the amount is sufficient to make it *prima facie* evidence, the triers of fact are warranted in coming to the conclusion that the accused was under the influence of intoxication from the proof of the content of alcohol in the blood alone. This type of statute is believed to be desirable, although in the actual trial of cases it may be very helpful to use an expert to give opinion testimony to the same effect. Furthermore, as the expert will ordinarily be in court to give the result of the blood or body fluid analysis he should give further assistance in expressing his opinion, which, along with the instructions of the judge as to the *prima facie* case, should carry great weight.

The law has generally moved at a slow pace compared with the advance of science. It is hardly to be expected that fluid tests to determine intoxication will at one stroke be accepted as good law. Progress in the law in a large measure is an unfolding process which follows the general public acceptance of changing ideas and principles. Legal development comes through the courageous effort of forward-looking judges and law-makers who see the need of adapting the law to the growing discoveries of science and the growing needs of state and society. By and large the courts have displayed a fair consideration of fluid tests and have generally held them admissible as evidence. This should be encouraging even in the face of the decisions which have been disturbed by the compulsory aspects of the test. In the course of time these views will undoubtedly change. Many things in the law of evidence which 50 years ago were looked upon with doubt and suspicion are accepted as the general rule today without question. As science improves and as the results of earlier experimentation become more firmly accepted the courts undoubtedly will respond. It is doubted now if, after full study of the problem, many courts will regard the taking of fluid tests as being precluded by the constitutional provisions against unlawful search and seizure, self-incrimination, or due process of law as it relates to the right of privacy.

CERTAIN MEDICAL AND LEGAL PHASES OF EUGENIC STERILIZATION ¹

By ABRAHAM MYERSON, M D , *Boston, Massachusetts*

EVERY program which proposes a reformation of society, whether in its biologic or sociologic structure, awakens fierce controversy which is usually independent of the merits of the situation. This controversy becomes the greater whenever sex or reproduction becomes the focus of the reform, since nowhere in the tangled web of human emotion and ideology is there more non-rationally based conduct than in this field. Therefore, it is to be expected that the points of view concerning eugenic sterilization disregard the essentials of proof and, like politics, the camps of the proponents and opponents of sterilization find strange bed-fellows.

There are grave weaknesses, as well as indisputable strength, in the postulates of those who favor eugenic sterilization. In the first place, there are large, relatively unexplored territories in psychiatry within whose universe of discourse belong the major number of people who are to be sterilized. Secondly, genetics itself is an evolving science which as yet has little substantial fact and understanding to explain the mechanisms of the inheritance of the mental diseases and the mental aberrations. Thirdly, and this, like the preceding two themes, will be elaborated, a reform of drastic nature must in a democracy have behind it a solid and educated public opinion, else it will not be enforced in any thorough-going way and, moreover, attempts at enforcement will lead to widespread social corruption and disunity.

Let us first consider the present day knowledge of psychiatry concerning those clinical groups in which sterilization is advocated. The psychiatrist is like the keeper of a zoo. He deals with diseases of different genesis and of varying degrees of substantial knowledge. These diseases are only united by the common fact of abnormal mentality, since the mental change under consideration may come from such diverse sources as the failure in sugar metabolism (pyruvic acid feeble-mindedness), syphilis, alcohol, endocrinal disorder, injury to the brain of whatever source, the changes of old age, and may even be entirely unknown as to etiology ¹. We may exclude at once from genetic relationship the best known of the diseases with which psychiatry deals as fundamentally environmental in cause or so closely wrapped up with normal processes as to be mere accentuation of retrogression. It is highly significant that the diseases which are best known are non-hereditary in their genesis and that the diseases which are fundamentally unknown as to pathology and physiological mechanism are ascribed to heredity. "All cats look gray in the dark," and it is easy to postulate a unifying mechanism—heredity—where little is known, and this is a temptation hard to resist.

¹ Received for publication February 13, 1943

Thus, general paresis, or, as it is officially known, dementia paralytica, is due to syphilis. True, there has been a valiant effort made to find a genetic basis for the susceptibility of any individual to brain disease following a syphilitic infection, since only 5 per cent of the total number of people infected by syphilis develop general paresis. In this connection it must be stated that logically there *must* be a constitution which permits any pathological change to occur. A stone cannot be infected by tuberculosis and even some species of animals have a constitutional inherited invulnerability to this disease, whereas other species are easily infected. But beyond syphilitic infection there is nothing to indicate that the individual who develops general paresis is fundamentally different from the mass of mankind, and from a practical standpoint it can be stated that whatever constitution is involved, syphilis is the essential factor in the multifactorial pattern by which the changes in the brain are brought about, and treatment remains the same regardless of any hypothetical constitution.

The situation is the same in that great bulk of mental diseases ascribable to arteriosclerotic brain changes and to the development of those plaques within the brain which bring about senile dementia. If any man lives long enough, he will develop an arteriosclerotic dementia or a senile dementia. No one as yet has been hardy enough to advocate sterilization to prevent the development of those mental diseases of the late fifties, sixties and seventies which are due fundamentally to the organic changes which take place with the passage of time.

The situation is somewhat more complex when we turn to the alcoholic mental diseases. Chronic alcoholism, by which these mental diseases are brought about, may be constitutional^{2, 3, 4, 5, 6, 7, 8}. Certain facts, which I have published elsewhere, indicate that the chronic alcoholic belongs to no definite personality type, that the amount of chronic alcoholism varies with race and social culture, with the pressure of tradition and the general habits of a community^{9, 10, 11}. If there is inheritance as a basis of chronic alcoholism, it is too vaguely demonstrated to be of any scientific value.

So, without considering other mental diseases of known origin, we may turn at once to those diseases for the prevention of which eugenic sterilization has been advocated on the ground of hereditary causation.

Schizophrenia is the first of this group of diseases to be here considered. Unfortunately, there is no clinical definition of this condition which is universally accepted, and error in diagnosis, especially in differentiating it from manic-depressive psychosis, occurs very commonly^{12, 13, 14, 15, 16}—to the point where it can safely be said that individual idiosyncrasy on the part of the psychiatrist is a factor in diagnosis. No one knows its pathology despite heroic efforts and the development of many theories, although it is only fair to say that there is a moderate accumulation of facts concerning its physiology¹⁷⁻²².

The foregoing is true of another major problem of psychiatry—the manic-depressive states. The typical manic-depressive state presents a clear-cut syn-

drome, but there are many cases in which the diagnosis remains in doubt even after years of study and observation. These cases blend with the neuroses and also with schizophrenia. Both the depressive and the manic phases often seem like accentuations of normal temperament, and it is quite certain that there is some degree of relationship to temperamental type, although the work of Kretschmer³³ ascribing a relationship to a pyknic body form can at this time be discarded as non-relevant. Little is known of its pathology or its physiology,^{34, 35} and it seems definitely to occur without any specific environmental precipitation,^{36, 37} just as does schizophrenia.

Here are two important groups of diseases which seem hereditary, yet the hereditary mechanism by which they are passed from one generation to another is unknown, and so is their essential psychopathology and organic physiological basis. For if they are hereditary, they must have an organic-physiologic basis, since we cannot scientifically conceive of mind passed from generation to generation without physical structure.

What has been here stated of schizophrenia and manic-depressive psychosis is also true of the groups of conditions lumped together as feeble-mindedness. The various types of feeble-mindedness are united only by the fact that the individuals concerned are incapable of normal learning by reason of a postulated congenital defect in intelligence³⁸⁻⁴⁰. The mental defects vary in degree from that of the idiot, who is beneath the level of a reasonably intelligent two-year old child, to that of the imbecile, who rarely if ever at all can learn to read and write, and the moron whose level of intelligence, although it permits him to carry on some work in the world, never evolves to a point where he is capable of handling abstract ideas, learning anything much beyond the range of his own immediate experiences which are extremely limited, and who can take up only those occupations and activities which involve the exercise of a very limited memory, a lessened skill and an inferior judgment. But this classification is not in terms of cause, since it only measures degrees of deficiency and has no relationship to causation. An individual suffering from the Mongolian type of feeble-mindedness may have the same level of intelligence as a cretin, but cause and pathology are very different in the two cases.

Thus, feeble-mindedness may arise from deficiency of the thyroid gland (cretinism),⁴¹ difficulty in the sugar metabolism (pyruvic acid metabolism),⁴² failure of the glands to develop as in Mongolian idiocy,⁴³ and many forms of pituitary disorder,⁴⁴ birth injury,⁴⁵ encephalitis occurring early in life,⁴⁶ injury to the growing and developing brain by reason of whooping cough,⁴⁷ and so through a long list of failures or injuries of body organs and brain. This is to say nothing of the accumulated defects which are known to arise through starvation, vitamin deficiency, extremely bad environmental conditions and the like^{48, 49, 50, 51, 52}.

No animal breeder, however much he laid his emphasis on breeding and heredity, would think of subjecting the animals with which he was concerned to the cruel, stupid and harsh conditions which constitute the life situation

of a great many of the children of mankind Yet it is precisely in the field of the feeble-minded that the eugenists have laid most of their emphasis upon the need for sterilization, and many myths have been developed in the field of feeble-mindedness which have no scientific basis whatever Elsewhere⁵⁷ I have criticized adversely, perhaps harshly, the work which has built up the "royal families" of the feeble-minded, the Nams, the Kallikaks, the Jukes, the Tribe of Ishmael, the Virginians, the Mongrels, etc Without in the least denying the important rôle of heredity, it can only be stated that low cultural level, especially occurring in sequestered groups, has been called feeble-mindedness on very scanty and insufficient evidence—evidence which any court of law would throw out as the worst kind of hearsay and which science should not even consider

The bulk of feeble-mindedness is utterly unknown as to genesis, pathology and disorder of physiology I lay emphasis upon this because it is insufficient to say "heredity is a cause," since heredity is no unified set of mechanisms If we say diabetes is inherited, we can at least define diabetes in terms of sugar metabolism We can test the sugar metabolism of the ancestors and descendants, as well as of the siblings and collaterals The diagnosis can be definitely and completely made Even if we do not understand the complete genesis of diabetes on a physiological basis, we do know that disorder of the pancreas and very likely of the pituitary body, as well as the cortex of the adrenal, plays important rôles

When we turn from these vaguely known diseases and ascribe them to heredity, we are at least in part explaining one unknown by another The science of genetics has largely been built up by animal experimentation, and the work can only be called brilliant and far-reaching The establishment of Mendelian laws, the evolution of the theory of the gene, represent two great landmarks in the history of the understanding of the mechanisms by which like begets like and by which variations appear^{58, 59, 60, 61, 62, 63, 64} But this work is only in its beginnings It is changing rapidly There is a growing body of evidence to show that Mendelian laws explain only variations—what I have called "adjectival" attributes rather than the "nouns" of quality⁶⁵ Thus, Mendelian laws explain the greenness and the smoothness of pea pods, but they do not explain the universal occurrence of pods which seems to be independent of Mendelian laws

Much work has been done in the field of physiological genetics to show that environment at all times plays a rôle in the evolution of hereditary qualities and in their evocation, and that a drastic change of environment may call into play what seem like opposing or at least markedly different hereditary qualities⁶¹ Experiments of far-reaching importance have shown that slowing up or accelerating the series of those timed evolutionary changes, by which the fertilized egg becomes an individual of a species, alters drastically the development of the individual^{58, 66} There may be, and I believe there is sick germplasm^{67, 68} which lasts over a considerable span of generations and adversely affects generation after generation To separate environment

from heredity is a useful dichotomy, but one which becomes pernicious when it becomes viewed as an absolute fact rather than as an abstraction of the human mind.

It is interesting to note that certain groups of people tend to become strict hereditarians and thus to view failure in life and the occurrence of disease as evidence of congenital inferiority. Conservative groups, as a rule, take this point of view. On the whole, these people are well satisfied with the status quo. They do not like the idea that their success and the failure of others may be accidental and environmental. The arrogant and the proud tend to be hereditarians and to neglect the environment entirely. Thus, a leading feature of Nazi ideology is the importance of blood, and all the studies which emanate from Germany have emphasized racial superiority, stock superiority and eugenics^{60, 70, 71}. They have not hesitated to sterilize and to destroy those whom they regarded as inferior in race and of inferior germplasm and constitution. Curiously enough, this ideology favors war which is by far the greatest cogenic factor in the world, since the best are sent out to be destroyed.

The biologists as a group, although with notable exceptions,^{61, 62} have tended to emphasize the germplasm largely because their experiments are carried out isolated so far as possible from the environment. They deal with animals of simple type and have mainly concerned themselves with the inheritance of simple qualities of bodily type rather than with the complex human attributes and that complexity of complexities—the human mind. They have tended to oversimplify the problem. Furthermore, those who have been impressed by the hopelessness of much of the therapeutics of psychiatry, who have been appalled by the rising cost of caring for the mentally sick, the epileptic, the feeble-minded and the criminals have sought the impatient reform and have advocated sterilization more from despair than from real understanding.

If we turn to those who oppose eugenics,⁷⁰ we find here, too, a curious conglomeration of bed-fellows. The Roman Catholic Church has laid down in the Encyclical of Pope Pius XI⁷² the basic proposition that sterilization is a mutilation which is not a punishment for crime and, consequently, an invasion of the sacred rights of man. Thus, a theologic concept is made the basis of opposition to what is essentially a biologic social reform. This point of view may be linked up with the attitude of the Church towards birth control, namely, that there must be no interference with procreation. It is curious that the Church, which insists on celibacy in its ministers and officers, is the most ardent advocate of unrestricted population increase.

On the other hand, the Bolshevik ideology, which in so many respects is anathema to the Catholic Church and which at least in its earlier development was completely opposed to religion, is also an enemy of eugenic sterilization and stresses environment, since this is in line with the general principle of economic determinism as fundamental in shaping the mind as well as the destinies of mankind. It is in general distasteful to Bolshevik science to at-

before discharge or parole from a state hospital. Up to January, 1935, 276 sterilizations (112 males and 164 females), or about 46 a year had been performed

(5) Oklahoma. A compulsory law was passed in 1931. Up to January, 1935, eight operations had been performed (one male and seven females). No comment!

(6) Washington. A voluntary law was passed in 1921. Up to January, 1935, 30 operations had been performed (24 females and 6 males).

Therefore, it is clear that if sterilization laws of any type are to be passed, even though the scientific proof be incontestible, public education as a preliminary is essential.

Certain myths must be dispelled in order to view our problem realistically: first, that the number of insane is increasing by leaps and bounds and, therefore, the race is threatened in a serious way by the propagation of the unfit.⁷⁷⁻⁸⁰ It is true that the admission rate to hospitals for mental disease has gone up enormously within the past few generations.^{1, 14, 87, 88, 89, 90, 91, 92, 93} But let us suppose that in China there were no hospitals, then the admission rate would be nil. As hospitals were built and the oriental members of the community became conscious of mental disease as something treatable, and if they regarded the hospitals favorably, the admission rate would go up from zero to a point which finally reached the real incidence of committable or hospitalizable mental diseases. This is actually what has taken place in some communities in America and which is taking place in some other parts of the world.

If we take two American states, Massachusetts and New York,⁹¹ as representative of communities with well established hospitals and with a reasonably good understanding of mental disease, we find that in these two states the commitment rate has changed but little during the past 20 years. Moreover, this is true of England, Wales and New Zealand.⁹³ There are cogent reasons why mental disease would not be expected to increase in the more enlightened communities of the United States and Europe.

In the first place, the marriage rate tends to be low in most of the important and transmissible mental diseases.^{95, 96, 97, 98, 99, 100} Secondly, the death rate is high.^{71, 84, 101, 102, 103, 104, 105} Third, the birth rate is low, contrary to the usual opinion.^{1, 43, 99, 106, 107, 108, 109} This is in part a resultant of the lower marriage rate and the greater death rate, but is to some extent independent of it. Fourth, even the divorce rate¹¹⁰ is higher among the mentally sick.

All these factors can be easily understood. Marriage acts as a barrier to the unsuccessful, the unattractive, the odd and the peculiar, and those who create unfavorable reactions. Moreover, in many of the mentally sick there is a lessened sexual drive. The divorce rate should be higher, too, since life with a person of unstable temperament and on the road to a mental disease is very difficult and often unbearable, so that divorce often takes

place before the psychosis shows itself in recognized form. Since the conditions of life tend to be worse for the mentally sick than for the mentally well, and because the general health suffers with most mental diseases, and finally because there is undoubtedly a general biologic defect as well, the death rate would be expected to be greater.

In the case of the feeble-minded the above holds true, even though it runs quite completely counter to the unscientific studies represented by the Nams, the Kallikaks, the Jukes, etc. I refer the reader to the British Report of the Departmental Committee on Sterilization,¹⁰⁸ which flatly declares that the prolificity of the feeble-minded is a myth, and also to the paper by Walter E. Fernald¹¹¹ which shows that in the case of the discharged and known feeble-minded from an institution in Massachusetts, there was a low marriage rate and a very low birth rate. What is mistaken for the high birth rate of the feeble-minded is the high birth rate of low cultural level. Statistics collected by Elkind and myself,⁴⁸ as well as by Popenoe,^{100, 109, 110} indicate, first, that the feeble-minded tend on the whole to come from families representative of the community as a whole, and secondly, there is not an unbalanced or disproportionate birth rate. Dayton's statistics^{108, 101, 102, 112} indicate very clearly that the death rate among the feeble-minded is proportional to the degree of feeble-mindedness and is greater than that of the normal population.

It is, I believe, safe to say that the vital statistics disclose the factors which operate against any considerable increase of the mental diseases and of feeble-mindedness. It is also true that we have become much more conscious of these conditions. A defective individual might adjust to a simple pastoral life but not be competent to meet the stresses of a civilization which demands the ability to learn to read, write, calculate and carry on relatively complex mental processes. A feeble-minded shepherd would not be particularly noticed, but a moron trying to operate machinery would show his defectiveness very quickly.

I here summarize the report of the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization,¹¹³ of which committee I was chairman and of which it is only fair to say that I was the worker mainly responsible for the report. Based on a review of the world's literature, and more especially of the recent work since the older writings have only historic value in this complex field, and with especial consideration of the fine studies of those touchstones of modern genetics, the monozygotic (or identical) twins, this^{15, 114, 115, 116, 117, 118, 119, 120, 121} Committee reached the following conclusions:

(1) Schizophrenia has an inherited basis¹²²⁻¹²² although this is not the entire story, and there is very likely an environmental root or factor of some kind which at present is entirely unknown.

(2) The same is true in about equal measure of manic-depressive psychosis.^{123, 124}

(3) It can be stated of feeble-mindedness that the bulk of it rests on a hereditary basis of some type, that there is an inheritance to intelligence although not of the "like begets like" variety, since despite the fact that there are families of feeble-minded, the bulk of the feeble-minded—according to reliable work—comes from families which are on the whole representative of the total community in social standing, achievement and general intelligence. This is certainly true of the cases one sees in private practice where sporadic feeble-mindedness frequently appears among groups of the highly intelligent and where relative feeble-mindedness—in the sense that an individual, although he develops above the level of the accepted standard for the feeble-minded, is, compared to the advantages and the group among whom he has lived, definitely deficient in intelligence—represents by far the greatest part of feeble-mindedness. Nevertheless, and excluding the work obviously faulty, no serious worker in the field of feeble-mindedness doubts that a great deal of mental deficiency, if not the most of it, is congenital and probably hereditary in origin ^{1, 40, 42-44, 48, 144-153}

(4) Of epilepsy the Report ¹⁵¹ stated that there was some constitutional etiologic basis, but that it was not proved to be of hereditary origin ^{155, 156, 157, 158, 159, 160}. Recent work has tended to show that there may be more of a hereditary basis than we assumed to be the case. This depends upon the study of the brain waves and is the product of a notable Boston group of workers, Lennox, Gibbs and Gibbs ^{161, 162, 163, 164}. I believe that the study of brain waves has not reached the precision and reliability which these workers assume it to have, nor do I agree that the kind of brain wave they describe is limited to epilepsy, so that their studies showing abnormal brain waves in the parents, collaterals and siblings of epileptics, which they assume prove the hereditary basis of epilepsy, are not so well founded as one might believe to be the case at first glance. An important paper attacking their assumptions in this matter is that of Finley and Dynes ¹⁶⁵. Epilepsy, or, more precisely, the convulsive states, appears to be producible in all forms of life beyond the most primitive, can be brought about in any human being by drugs, electricity, and brain damage, and so differs radically from schizophrenia and manic-depressive psychosis. The most that as yet can be said as to its relationship to heredity is that some individuals and familial groups are more liable to it.

(5) So far as crime is concerned, this being one of the conditions which ardent eugenists expect to be reduced by sterilization, ^{70, 77, 106, 107, 168, 169, 170, 171, 172, 173} I can only say that this Committee rejected in general the hereditary nature of most of crime ⁷³. There are too many social variables in crime for it to be accepted as an essentially biologic condition. It may well be that some criminals are abnormal variants. This is surely not true of all of them, and the studies which have purported to prove this have, on the whole, been too precariously based on the shape of ear lobes, height, weight, head-form to have reached a place worthy of the name scientific at this time. There are individuals who lack social feeling, who are crass and crude ego-

tists, who find conformity difficult, and such individuals are found at the top of the social ladder among the successful as well as at its bottom and among those who are incarcerated in jails

At this point, one may bring up the question of the existence of a psychopathic society^{174, 175, 176} Adjustment to any society is normal or represents normality only if it can be assumed that the demands of that society are in conformity with the essential drives, instincts and evolution of the normal man For example, our society emphasizes acquisitiveness and over-rewards the pathologically acquisitive, since, as Aldous Huxley says, there are as many perversions of the acquisitive instinct as there are of the sexual That there may be conflict of biologic and social demand can be cogently exemplified by the case of a 16-year old girl who has become pregnant without the formality of marriage, but who is biologically normal although socially maladjusted, whereas the social worker who looks after her, a virgin aged 50, is biologically abnormal although socially adjusted Society is not at all rational about sex, marriage, work, pleasure-seeking, entertainment and achievement in general It is doubtful if he lives best who works all day long, is humble, frugal and passively law-abiding A non-conformist rebel who gets into all kinds of social trouble may be and often is a better human specimen

Our Committee, taking into account the social structure of our times, the prejudices and taboos which reign, the conflict and the welter of opinion, came to conclusions which are here stated in abridged form We accept as a reasonable working hypothesis that certain of the mental diseases rest on a constitutional and a hereditary basis, and that a program of eugenic sterilization is indicated and desirable These diseases, excluding from consideration at this point the very rare neurologic disorders,¹⁷⁷ such as Huntington's chorea, Friedreich's ataxia, myotonia, etc., are schizophrenia, manic-depressive psychosis, most of the forms of feeble-mindedness, and possibly epilepsy We advocate, therefore, the passage of voluntary laws to apply to certified cases of these diseases, either within private or public hospitals or cared for in the community

The most important conclusion is that neither the psychiatrist nor the eugenicist can afford to be dogmatic in his opinion What is needed most of all is an organized research, preferably by some great governmental agency and the ideal agency would be the United States Public Health Service This research might well take the following main directions

First, coordinated long-time studies on the epidemiology, psychology, physiology, chemistry and physics of the patients who form the subject matter of psychiatry Groups of specially trained men should be set free from economic pressure to devote their lives to such researches

Second, an institute organized for a continuing program of at least 100 years should be established for the study of human heredity One man's life-time is not long enough because he lives only as long as his subjects.

and his working career is rarely more than 40 years. Several generations of people must be intimately known and their lives scientifically recorded before we can know much of human heredity. The workers in this institute should include not only scientists in each field which is pertinently involved, but also the best of statisticians as well as high-grade field workers capable of social investigation of an objective type.

It needs emphasis at this point that one of the cardinal assumptions of the rabid eugenicists,^{78, 88, 178, 179, 180} namely, that there is a fundamental antagonism between eugenics, or being well-born, and euthenics, or social betterment and amelioration, is not in its generality true. There are social ameliorations and euthenic measures which probably are not of value to the race and even hurt it. Thus, nursing along an obviously defectively constituted child so that he reaches maturity, can marry and procreate, certainly seems non-eugenic, even cacogenic. Furthermore, whatever steps we take for the cure of, let us say, schizophrenia, should be associated with eugenic measures and if we do finally, as I believe we will, discover methods for the cure of schizophrenia, manic-depressive psychoses and others of the mental diseases, it may be of great importance to establish sterilization as a condition of treatment, unless it can be shown that the curative measure also cures the germplasm, which at first blush seems unlikely.

In its broader scope, however, euthenics makes the race better rather than worse. An epidemic has no particular predilection for the unfit.^{181, 182} It merely carries off those less resistant to it, and this does not bear any relationship whatever to our human values of fitness and unfitness. Moreover, epidemics, malnutrition, and the serious adverse conditions under which many of the people of the world live very definitely injure otherwise sound persons, and/or prevent the full development of hereditary potentiality. Accident, disease, social privation and cacothenic influences are not disguised eugenic measures. In fact, it is possible—and without any scientific warrant I believe this to be the case—that they injure germplasm. There is no reason to believe that the germplasm,—that is, the chromosomes and genes—, as well as the rest of the egg and the seed, may not be injured by the same illness that affects the heart, the lungs, or the brain of the individual. The program of euthenics may, therefore, be considered a part of eugenic betterment, and legislation which provides the best of food and housing, sunshine, reasonable hours of employment and adequate compensation, social insurance of necessary kinds, as well as good medical care, although it may be defined as euthenic, is also eugenics of a positive type.

It is time medical biology and law made some kind of a formal alliance with a division of labor and a unified purpose for the social good. The division of labor can be compared to the two different and collaborative functions of the nervous system. Science, as one of the partners, has for its business the sensory function, that is, it gathers the information by scientific technics, analyzes its experiences and experiments according to statistical methods, and so reaches proved conclusions. The job of putting the indi-

cated program of social reformation into activity—the motor function—belongs to law. Having assured itself that the propositions evolved by science are solidly established and accepted, to it belongs the task of manipulating the unyielding and prejudiced society into line. Whatever laws it passes must be capable of being enforced, for however good scientific theory and postulates may be, there are social principles of conduct, taboos, unreasonable attitudes and non-rational traditions which must be taken into account. Other rights of the individual must not be violated even though to do so seems to be a short cut to reform. The law or, more personally put, the legislators and the executive and legal directors of society have the duty to be equitable and practical at one and the same time in such a matter as eugenic sterilization. Science must gather the material and present the facts. Law, especially in a democracy, must possess the guilelessness of the dove and the wisdom of the serpent in framing suitable legislation and workable technics for their operation in the particular society within whose framework the reformation is to be wrought.

REFERENCES

- 1 DAYTON, N. A. New facts on mental disorders. Study of 89,190 cases, 1940, C. C. Thomas Co., Springfield, Illinois.
- 2 BLUM, AGNES. Darf die Erbllichkeit der Alkoholschaden als bewiesen gelten? (Is the heredity of alcohol damage proven?), *Ztschr. f. Sexualwissenschaft*, 1931, xviii, 145-151.
- 3 DIEM, O. Die psychoneurotische erbliche Belastung der Geistesgesunden und der Geisteskranken, *Arch. f. Rass u. Gesselsch. Biol.*, 1905, ii, 89.
- 4 ELDERTON, E., and PEARSON, K. A first study of the influence of parental alcoholism on the physique and ability of the offspring, *Eugen. Lab. Mem.*, 1910, 10.
- 5 MOORE, M. Alcoholism: some contemporary opinions, *New England Jr. Med.*, 1941, ccxliii, 848-857.
- 6 MYERSON, A. The inheritance of mental diseases, 1925, Williams & Wilkins Co., Baltimore, pp. 35-36.
- 7 PETER, W. W. Germany's sterilization program, *Am. Jr. Pub. Health*, 1934, xxiv, 187-191.
- 8 TILLOTSON, K. J., and FLEMING, R. Personality and sociologic factors in the prognosis and treatment of chronic alcoholism, *New England Jr. Med.*, 1937, ccxvii, 611-615.
- 9 EVERTON, H. (ed.) *Alcohol and man*, 1933, The Macmillan Co., New York.
- 10 HAGGARD, H. W. and JELLINEK, E. M. *Alcohol explored*, 1942, Doubleday, Doran & Co., Inc., New York.
- 11 MYERSON, A. The social psychology of alcoholism. *Dis. Nervous System*, 1940, i, 1-8. Alcohol: a study of social ambivalence, *Quart. Jr. Studies on Alc.*, 1940, i, 13-20. Alcoholism and induction into military service, *Quart. Jr. Studies on Alc.*, 1942, iii, 204-220.
- 12 BANCROFT, C. P. Is there an increase amongst the dementing psychoses?, *Trans. Am. Medico-Psych. Assoc.*, 1941, xli, 286.
- 13 DOERING, C. R., and RAYMOND, ALICE F. The reliability of observation in psychiatric and related characteristics. In "Schizophrenia: Statistical studies from the Boston Psychopathic Hospital" 1925-1934, pp. 249-257.
- 14 ELKIND, H. B. Are mental diseases on the increase? The problem of determination. *Psychiat. Quart.*, 1939, xiii, 165-172.

- 15 EIKIND, H B, and DOERING, C R The application of statistical method to the study of mental disease In "Schizophrenia Statistical Studies from the Boston Psychopathic Hospital, 1925-1934," pp 55-63
- 16 MYLSON, A Are mental diseases on the increase? Psychiat Quart, 1939, xiii, 177, Errors and problems in psychiatry, Ment Hyg, 1940, xxiv, 17-35
- 17 ANGYAL, A, FREEMAN, H, and HOSKINS, R G Physiologic aspects of schizophrenic withdrawal, Arch Neurol and Psychiat, 1940, xlv, 621-626
- 18 BOWMAN, K M, and RAYMOND, ALICE F Physical findings in schizophrenia, Am Jr Psychiat, 1929, viii, 901-913
- 19 BRICE, A T The blood fats in schizophrenia, Jr Nerv and Ment Dis, 1935, lxxxi, 613-632
- 20 CARMICHAEL, H T, RHEINGOLD, J C, and LINDER, F E The bromide permeability test in schizophrenia, Jr Nerv and Ment Dis, 1935, lxxvii, 125-133
- 21 ELVIDGE, A R, and REED, G E Biopsy studies of cerebral pathologic changes in schizophrenia and manic-depressive psychosis, Arch Neurol and Psychiat, 1938, xl, 227-264
- 22 FINESINGER, J E, COHEN, M E, and THOMSON, K J Velocity of blood flow in schizophrenia, Arch Neurol and Psychiat, 1938, xxxix, 24-36
- 23 FREEMAN, H The arm-to-carotid circulation time in normal and schizophrenia subjects, Psychiat Quart, 1934, viii, 290-299
- 24 GAMPER, E, and KRAL, A Experimentell-biologische Untersuchungen zum Schizophrenieproblem, Ztschr f d ges Neurol u Psychiat, 1933, cxlvi, 567-598
- 25 GELLHORN, E Experimental investigations on the influence of hypoglycemia on the central nervous system and their significance for the treatment of dementia praecox, Proc Institute of Medicine of Chicago, 1938, xi, 5, The action of hypoglycemia on the central nervous system and the problem of schizophrenia from the physiologic point of view, Jr Am Med Assoc, 1938, cx, 1433-1434, Effects of hypoglycemia and anoxia on the central nervous system, a basis for a rational therapy of schizophrenia, Arch Neurol and Psychiat, 1938, xl, 125-146
- 26 GJESSING, R Beitrage zur Kenntnis der Pathophysiologie des katatonen Stupors, Arch f Psychiat, 1932, xcvi, 319-473, 1935-1936, civ, 355-416, 1938-1939, cix, 525-595
- 27 GOTTLIEB, J S, and LINDER, F E Body temperatures of persons with schizophrenia and of normal subjects, Arch Neurol and Psychiat, 1935, xlviii, 775-785
- 28 HIMWICH, H E, BOWMAN, K M, WORTIS, J, and FAZEKAS, J F Biochemical changes occurring in the cerebral blood during the insulin treatment of schizophrenia, Jr Nerv and Ment Dis, 1939, lxxix, 275-295
- 29 LINTON, J M, HAMELINK, M H, and HOSKINS, R G Cardiovascular system in schizophrenia studied by the Schneider method, Arch Neurol and Psychiat, 1934, xxvii, 712-722
- 30 LEWIS, N D C Research in dementia praecox (past attainments, present trends and future possibilities), National Committee for Mental Hygiene, New York, 1936
- 31 LOONEY, J M, and FREEMAN, H Oxygen and carbon dioxide contents of arterial and venous blood of schizophrenic patients, Arch Neurol and Psychiat, 1938, xxxix, 276-283
- 32 SLEEPER, F H, and JELLINEK, E M A comparative physiologic, psychologic, and psychiatric study of polyuric and non-polyuric schizophrenic patients, Jr Nerv and Ment Dis, 1936, lxxxiii, 557-563
- 33 KRETSCHMER, E Korperbau und Charakter, 1920, J Springer, Berlin, Physique and character, 1925, Harcourt-Brace, New York, Heredity and constitution in etiology of psychic disorders, Brit Med Jr, 1937, ii, 403-406
- 34 PEARL, RAYMOND Constitution and health, 1933, Kegan Paul, Trench, Trubner & Co, Ltd, London
- 35 STOCKARD, C R Constitution and type in relation to disease, Medicine, 1926, v, 105

- 36 BUMKE, Q Discussion of Faltshäuser's paper Zur Frage der Sterilisierung geistig Abnormer, Allg Ztschr f Psychiat, 1932, xcvi, 372
- 37 POLLOCK, H M, MALZBERG, B, and FULLER, R G Hereditary and environmental factors in the causation of dementia praecox and manic-depressive psychoses Chapt II Do Mendelian laws apply to the inheritance of manic-depressive psychoses? Psychiat Quart, 1934, viii, 337-371
- 38 BRUGGER, C Die Vererbung des Schwachsinn's, Handb Erbbiol, 1939, v (Part 2), 597-768
- 39 DAVIES, S P Social control of the feeble-minded, The National Committee for Mental Hygiene, New York, 1923
- 40 GODDARD, H H Feeble-mindedness, its cause and consequences, 1923, The Macmillan Co, New York
- 41 LUXENBURGER, H Endogenous feeble-mindedness and sex linked heredity, Ztschr f d ges Neurol u Psychiat, 1932, cxi, 320-332
- 42 MIERSON, A Nature of feeble-mindedness, Am Jr Psychiat, 1933, xlii, 1205-1226
- 43 MIERSON, A, and ELAIND, H B Researches in feeble-mindedness, Bull Massachusetts Dept Mental Diseases, 1930, vii, 108-229
- 44 PEARSON, K On the continuity of mental defect, 1914, Dunlau & Co, London
- 45 ROSSANOFF, A J The etiology of mental deficiency with special reference to its occurrence in twins, Psychol Monogr Whole No 216, 1937
- 46 MOTT, F Heredity in relation to mental disease and mental deficiency, Brit Med Jr, 1926, i, 1023-1026
- 47 WELLS, J, and ARTHUR, G Effect of foster-home placement on the intelligence ratings of children of feeble-minded parents, Ment Hyg, 1939, xliii, 277-285
- 48 WILDENSKOV, H O Investigations into the causes of mental deficiency (Trans from Danish by Hans Andersen), 1934, Oxford University Press, London
- 49 WOODALL, C S The children of mentally defective and mentally retarded mothers, Proc 56th Ann Session of Am Assoc for Study of Feeble-minded, May 26, 1932
- 50 JERVIS, G A Genetics of phenylpyruvic oligophrenia contribution to study of influence of heredity on mental defect, Jr Ment Sci, 1939, lxxv, 719
- 51 LURIE, L A, and LEVY, S Personality changes and behavior disorders of children following pertussis A report based on the study of five hundred problem children, Jr Am Med Assoc, 1942, cx, 890-894
- 52 FREEMAN, F N, HOLZINGER, K. J, and MITCHELL, B C The influence of environment on the intelligence, school achievement, and conduct of foster children twenty-seventh Yearbook of the National Society for the Study of Education, 1928, pp 103-218
- 53 PATON, D N, and FINDLAY, L Poverty, nutrition and growth Studies of child life in cities and rural districts of Scotland, His Majesty's Stationery Office, London, 1926
- 54 ROBERTS, L The nutrition and care of children in a mountain county of Kentucky, Bureau Publication No 110, Government Printing Office, Washington, 1922
- 55 SKEELS, H M, UPDEGRAFF, R, WELLMAN, B L, and WILLIAMS, H M A study of environmental stimulation An orphanage preschool project, University of Iowa Studies in Child Welfare, 1939, vi, No 4
- 56 SKODAK, M The mental development of adopted children whose true mothers are feeble-minded, Child Development, 1938, ix, 303-308
- 57 MYERSON, P 77
- 58 GOLDSCHMIDT, R "Progressive heredity" and "anticipation," Jr Hered, 1938, xxi, 140-142 Physiological genetics 1938, McGraw-Hill Book Co, New York, 1938
- 59 HALDANE, J B S Heredity and politics, 1938, W W Norton & Co, Inc, New York, pp 24-25
- 60 HERTWIG, O Neue Untersuchungen ueber die Wirkung der Radiumstrahlung auf die Entwicklung tierischer Eier, Sitz d Kgl Preuss Akad d Wissenschaften, 1910, xxvii, Mitt, ii, 751-771 J Reimer, Berlin

- 61 JENNINGS, H S The biological basis of human nature, W W Norton & Co, Inc, New York, 1930, p 124
- 62 MORGAN, THOMAS The theory of the gene, 1926, Yale University Press, New Haven
- 63 MULLER, H J Artificial transmutation of the gene, Science, 1927, lxvi, 84
- 64 PATTERSON, J T X-rays and somatic mutations, J Hered, 1926, xvii, 137-143
- 65 MYERSON, A The relationship of hereditary factors to mental processes, Res Pub Assoc Res Nerv Ment Dis, 1939, xix, 16-49
- 66 RIDDLE, O The control of heredity, Proc Third Race Betterment Conference, January 2-6, 1928, p 62-71
- 67 FOREL, A Abstinenz oder Massigkeit, Grenzfragen Nerv-und Seelenbens, 1910, H 74
- 68 Eugenical sterilization, A reorientation of the problem By the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization, 1936, The Macmillan Co, New York, pp 75-78
- 69 LENZ, F Menschliche Erbliehkeitslehre und Rassenhygiene (Eugenik), 1932, J F Lehmanns, Munich, vol 2
- 70 MAYER, JOSEPH Gesetzliche Unfruchtbarmachung Geisteskranker Studien zur Katholischen Sozial- und Wirtschaftsethik, 1927, 3, Freiburg
- 71 RUDIN, E Studien ueber Vererbung und Entstehung geistiger Storungen, Monogr aus dem Gesamtgebiete der Neurol u Psychiat, 1916, J Springer, Berlin, p 45
- 72 PIUS XI Reconstructing the social order, Four Great Encyclicals, The Paulist Press, New York, p 95-97
- 73 BUCKLE, HENRY T History of civilization in England, 1857-1861, J W Parker & Son, London
- 74 HOBHOUSE, L T Morals in evolution, 1906, Henry Holt & Co, New York
- 75 ARNOLD, G B A brief review of the first thousand patients eugenically sterilized at the state colony for epileptics and feeble-minded, Proc Am Assoc Ment Def, 1938, xliii, 56-63
- 76 Eugenical Sterilization,⁶⁸ Chapter II
- 77 Human Betterment Foundation, Collected Papers on Eugenic Sterilization in California, Pasadena, California, 1930
- 78 DARWIN, CHARLES The descent of man and selection in relation to sex, London, 1882, pp 133-134
- 79 FARRAR, C B Social aspects of mental deficiency, Canad Med Assoc Jr, 1926, xvi, 1233-1238
- 80 HERD, H Sterilization of the mentally defective, Lancet, 1933, ii, 783-786
- 81 LANDMAN, J H The human sterilization movement, Jr Crim Law and Criminol, 1933, xxiv, 400-408
- 82 LAUGHLIN, H H Eugenical sterilization 1926, American Eugenics Society, New Haven, The legal status of eugenical sterilization, Supplement to the Annual Report of The Municipal Court of Chicago for the year 1929
- 83 MALTHUS, T R An essay on the principle of population, London, 1803
- 84 MEYER, H Besteht bei vererbbaeren Geisteskrankheiten, insbesondere beim Schizophrenie und manisch-depressivem Irresein ferner bei genuiner Epilepsie und Schwachsinn, eine erhohte Sterblichkeit in dem Sinne, dass die Fortpflanzung der Kranken verringert wird? Allg Ztschr f Psychiat, 1933, c, 48-61
- 85 SPENCER, H The principles of ethics, London and Edinburgh, 1892, i, 548
- 86 WATKINS, H M Selective sterilization, Bull Massachusetts Dept Ment Dis, 1932, xvi, 59-68
- 87 DORN, H F Incidence and future expectancy of mental disease, Pub Health Rep, 1938, lxi, 1991
- 88 LANDIS, CARNEY, and PAGE, JAMES Magnitude of the problem of mental disease, mental health, Publ of Am Assoc Advancement of Science, No 9, The Science Press, 1939, pp 149-155

- 89 Mental patients in State Hospitals 1926 and 1927, Government Printing Office, Washington, 1930
- 90 Patients in hospitals for mental disease 1935, Bureau of the Census, Government Printing Office, Washington, 1937
- 91 POLLOCK, H, and MALZBERG, B Trends in mental disease, *Ment Hyg*, 1937, xxi, 456
- 92 WILE, I S The threat of mental disease, *Jr Nerv and Ment. Dis*, 1940, xci, 323-342
- 93 WINSTON, E The assumed increase of mental disease, *Am Jr Sociol*, 1935, \1, 427-439
- 94 Eugenical Sterilization,⁶⁸ p 27 ff
- 95 DAYTON, N A Marriage and mental disease, *New England Jr Med*, 1936, ccxi, 153-155
- 96 MALZBERG, B Marriage rates among patients with mental disease, *Ment Hyg*, 1938, xxi, 634
- 97 Eugenical Sterilization,⁶⁸ p 43 ff
- 98 MYERSON,⁶ p 109 ff
- 99 POLLOCK, H M, and FURBUSH, EDITH H Comparative statistics of state hospitals for mental diseases, State Hospital Press, Utica, 1922
- 100 POPENOE, P Eugenical sterilization, *Jr Social Hyg*, 1928, i, 27 (See also Collected Papers)
- 101 DAYTON, N A Mortality in mental deficiency over a fourteen year period Analysis of 8,976 cases and 878 deaths in Massachusetts, *Proc of Fifty-fifth Annual Session of Am Assoc for Study of the Feeble-minded*, May 25-28, 1931
- 102 DAYTON, N E, DOERING, C R, HILFERTY, M M, MAHER, H C, and DOLAN, H H Mortality and expectation of life in mental deficiency in Massachusetts analysis of the Fourteen-Year Period 1917-1930, *New England Jr Med*, 1932, ccvi, 555-570, and 1932, ccvi, 616-631
- 103 Eugenical Sterilization,⁶⁸ p 51 ff
- 104 Mental Patients in State Hospitals, 1928, Government Printing Office, Washington, 1931
- 105 Mortality of Patients in Hospitals for Mental Diseases, *Statistical Bulletin of the Metropolitan Life Insurance Co*, v 19, no 5 (May) 1928
- 106 ESSEN-MOLLER Ueber die Fortpflanzung von Geisteskranken *Arch f Rassen-u Gesellsch-Biol*, 1936, xxx, 432-436
- 107 Eugenical Sterilization,⁶⁸ p 47 ff
- 108 Report of the Departmental Committee on Sterilization, His Majesty's Stationery Office, London, 1934
- 109 POPENOE, P Fecundity of the insane, *Jr Hered*, 1928, xv, 80
- 110 POPENOE, P Social and economic status of the sterilized feeble-minded, *Jr Applied Psychol*, 1928, xii, 304-316 (See also Collected Papers)
- 111 FERNALD, WALTER E After-care study of the patients discharged from Waverley for a period of twenty-five years, *Ungraded*, 5, 1919 (see Myerson,⁶ p 81)
- 112 DAYTON, N A Influence of size of family upon the characteristics of the mentally deficient, *Am Jr Psychiat*, 1935, xci, 799-832
- 113 Eugenical Sterilization,⁶⁸ pp 177-183
- 114 CARTER, H D Ten years of research on twins, contributions to the nature-nurture problem, *Yearbk Nat Soc Stud Educ*, 1940, xxxv, 235-255
- 115 NEWMAN, H H, FREEMAN, F N, and HOLZINGER, K. J TWINS a study of heredity and environment, University of Chicago Press, Chicago, 1937
- 116 ROSANOFF, A J, HANDY, L M, PLESSET, I R, and BRUSH, S The etiology of so-called schizophrenic psychoses, with special reference to their occurrence in twins *Am Jr Psychiat*, 1934, xci, 247-286
- 117 ROSANOFF, A J, HANDY, L M, and PLESSET, I R The etiology of manic-depressive syndromes with special reference to their occurrence in twins, *Am Jr Psychiat*, 1935, xci, 725-761
- 118 ROSANOFF, A J, HANDY, L M, and ROSANOFF, I A Etiology of epilepsy with special reference to its occurrence in twins, *Arch Neurol and Psychiat*, 1934, xcvi, 1165

- 119 SCHWTSINGLR, GLADYS C Heredity and environment, 1933, The Macmillan Co, New York
- 120 VIRSCHUPF, O VON Twin research from the time of Francis Galton to the present day, *Proc Roy Soc*, 1939, cxxviii, 62-81
- 121 WOODWORTH, R S Heredity and environment, a critical survey of recently published material on twins and foster children, *Bulletin 47*, Social Science Research Council, New York, 1941
- 122 GALACHYAN, A Similarity of psychoses in schizophrenic brothers and sisters in relation to heredity of schizophrenia, *Sovet Neuropat Psikhi i psikhigig*, 1933, ii, 91-103
- 123 GLAUS, A Die Bedeutung der exogenen Faktoren für die Entstehung und den Verlauf der Schizophrenie, *Schweiz Arch Neurol Psychiat*, 1939, xliii, 32-47
- 124 HOFFMANN, H Die Nachkommenschaft bei endogenen Psychosen, 1922, J Springer, Berlin, Vererbung und Seelenleben, 1922, J Springer, Berlin, Incidence of hereditary psychoses, schizophrenia and epilepsy in children of schizophrenics and epileptics, *Ztschr f d ges Neurol u Psychiat*, 1928, cxiv, 630-646
- 125 HOBGEN, L The interaction of heredity and environment, *Jr Ment Sci*, 1933, lxxix, 590-601 The analysis of pedigrees, in "The chances of morbid inheritance" (C P Blacker, ed), 1934, William Wood & Co, Baltimore, p 405
- 126 JUDA, A Incidence of dementia praecox in grandchildren of schizophrenics, *Ztschr f d ges Neurol u Psychiat*, 1928, cxiv, 630-646
- 127 KALLMANN, F J Heredity, reproduction and eugenic procedure in the field of schizophrenia, *Eugen News*, 1938, xxiii, 105-113, *Genetics of schizophrenia*, 1938, J J Augustine, New York
- 128 KOLLER, S Heredity in schizophrenia, *Ztschr f d ges Neurol u Psychiat*, 1939, clxiv, 199-228
- 129 LANGE, J Rôle of heredity in pathogenesis of schizophrenia, observations on uniovular twins, *Wien klin Wchnschr*, 1929, xlii, 1213 and 1247
- 130 LUXENBURGER, H Hereditary prognosis in schizophrenia, *Ztschr f psych Hyg*, 1933, vi, 131-135
- 131 POLLOCK, H M, MALZBERG, B, and FULLER, H G Hereditary and environmental factors in the causation of dementia praecox and manic-depressive psychoses Chapt III Family stock of dementia praecox patients, *Psychiat Quart*, 1934, viii, 553-599
- 132 WEINBERG, I Ueber neuere psychiatrische Vererbungsstatistik, *Arch f Rass u Ges-Biol*, 1913, 303-312 Prognostication of heredity and possibilities of morbidity among male and female relatives of schizophrenics, *Ztschr f d ges Neurol u Psychiat*, 1928, cxii, 101-171
- 133 BERZE, J Theory and hereditary aspect of manic-depressive insanity, *Psychiat Neurol Wchnschr*, 1930, lxxxi, 473-477
- 134 BLEULER, M Manic-depressive—heredity and hereditary prognosis in cross section of population, review of literature, 1933-1936, *Fortschr d Neurol Psychiat*, 1937, ix, 250-264
- 135 BRAUN, E Manic-depressive—Review of literature, *Fortschr d Neurol Psychiat*, 1937, ix, 380-390
- 136 BRUGGER, C Statistics of heredity of mental taints in average population, *Ztschr f d ges Neurol u Psychiat*, 1929, cxviii, 459-488
- 137 ESSEN-MOLLER, E Manic-depressive—fertility of certain groups of mentally diseased, *Acta psychiat et neurol*, 1935, suppl 8, pp 1-314
- 138 HUTTER, A Manic-depressive—heredity and hereditary prognosis, *Nederl tijdschr v geneesk*, 1934, lxxviii, 284-289
- 139 KRAEPELIN, E Manic-depressive insanity and paranoia, E & S Livingstone, Edinburgh, 1921
- 140 KRETSCHMER, E Familial forms of psychoses, *Munchen med Wchnschr*, 1933, lxxv, 1084

- 141 LUXENBURGER, H Erbprognose und praktische Eugenik im cyclothymen Kreise, *Nervenarzt*, 1932, v, 505-518
- 142 PASKIND, H A Hereditary factors in manic-depressive psychosis, *Arch Neurol and Psychiat*, 1930, xxiv, 747-752
- 143 SLATER, ELIOT Hereditary factors in manic-depressive psychosis, *Ztschr f d ges Neurol u Psychiat*, 1938, clxiii, 1
- 144 BAKER, G Mental and social status of 1600 patients in obstetrical clinic of Johns Hopkins Hospital, How this relates to problems of eugenics, *Bull Johns Hopkins Hosp*, 1933, lii, 275-314
- 145 BRUGGER, C Die Vererbung des Schwachsinn, *Handb Erbbiol*, 1939, v (Part 2), 697-768 *Fortschr Neurol Psychiat*, 1939, xi, 239-246
- 146 DOLL, E A Mental development and heredity, *Jr Consult Psychol*, 1940, vi, 243-244
- 147 ENGLISH, W M The feeble-minded problem, *Am Jr Psychiat*, 1931, xi, 1-8
- 148 Feeble-mindedness today, A review of some recent publications on the subject, *Jr Hered*, 1930, xxi, 421-430
- 149 HERD, H B Sterilization of the mentally defective, *Lancet*, 1933, ii, 783-786 Inheritance of mental deficiency in "The chances of morbid inheritance," 1934 (Chapt 5), William Wood & Co, Baltimore
- 150 McNEIL, C Heredity a minor factor in mental deficiency, *Brit Med Jr*, 1934, i, 584-585
- 151 TREDGOLD, A F Mental deficiency, 1929, Belliere, Tyndal & Co., London
- 152 PENROSE, L S Some genetical problems in mental deficiency, *Jr Ment Sci*, 1938, lxxxiv, 693-707
- 153 SHUTTLEWORTH, F K, ROSSNOFF, A J, HANDY, L M and PLESSET, I R On the etiology of mental deficiency, a critical appraisal, *Jr Educ Psychol*, 1938, xxi, 374-383
- 154 Eugenical sterilization,⁹⁸ pp 136-144
- 155 BRAIN, W R The inheritance of epilepsy, *Quart Jr Med*, 1925-1926, xli, 299-310
- 156 BURR, C W Heredity in epilepsy A study of 1449 cases, *Arch Neurol and Psychiat*, 1922, vii, 721-728
- 157 COBB, S Causes of epilepsy, *Arch Neurol and Psychiat*, 1932, lxxvii, 5
- 158 ECHEVERRIA, G On epilepsy, 1870, William Wood & Co, New York
- 159 STEIN, CALVERT Hereditary factors in epilepsy, *Am Jr Psychiat*, 1933, vii, 989-1027
- 160 THOM, D A. Epilepsy in the offspring of epileptics, *Boston Med and Surg Jr*, 1916, clxxv, 573-575, and 599-600
- 161 GIBBS, F A, DAVIS, H, and LENOX, W G The electroencephalogram in epilepsy and in conditions of impaired consciousness, *Arch Neurol and Psychiat*, 1935, lxxv, 1133
- 162 GIBBS, F A, GIBBS, E L, and LENOX, W G The electro-encephalogram in diagnosis and in localization of epileptic seizures, *Arch Neurol and Psychiat*, 1936, lxxvi, 1225
- 163 GIBBS, F A, and GIBBS, E L Atlas of electro-encephalographic records, 1940, Lew A Cummings, Cambridge.
- 164 LENOX, W G, GIBBS, E L, and GIBBS, F A The inheritance of epilepsy as revealed by the electro-encephalograph, *Jr Am Med Assoc*, 1939 cxi, 1002, *Arch Neurol and Psychiat*, 1940, lxxiv, 1155
- 165 FINLEY, KNOX H, and DINES, JOHN B Electro-encephalographic studies in epilepsy A critical analysis, *Trans Am Neurol Assoc*, 1942, William Bird Press, Richmond pp 90-92 (abstract)
- 166 CREUTZ, W Der Einfluss der erblichen Belastung und der Umwelt bei Criminellem *Allg Ztschr f Psychiat*, 1931 xci, 73-106
- 167 EAST, W N Heredity and crime, *Eug Rev* 1928 vi, 169-172
- 168 LANGE, J Verbrechen und Vererbung *Eug I*, 1931 165 *Verbrechen und Schicksal*, Leipzig, 1920 (English translation *Crime and Destiny* 1930, Boni, New York)

- 169 POMEROI, P Twins and criminals, Jr Hered, 1936, xxvii, 388-390
- 170 RINDL, M Sterilization of young and old criminals and descendants of criminals in light of new German law of July 14, 1933, significance for eugenics and for social prognosis, Arch f Kriminol, 1933, xcm, 125 and 238
- 171 STUMPH, F Kriminalität und Vererbung, Handb Erbbiol, 1939, v (Part 2), 1223-1274
- 172 PLOSCOWI, MORRIS Causes of crime, in "Wickersham Committee Report," 1930
- 173 Eugenical sterilization,^{os} pp 150-152
- 174 BURROW, T The structure of insanity a study in phylopathology, 1932, Kegan Paul, London, The biology of human conflict an anatomy of behavior, individual and social, 1937, The Macmillan Co, New York, The human equation, Ment Hyg, 1941, xxiii, 210-220
- 175 JASTROW, J (ed) The story of human error, 1936, D Appleton-Century Co, New York
- 176 KRAUS, A J I Sick Society, University of Chicago Press, Chicago, 1929
- 177 Eugenical sterilization,^{os} pp 145-149
- 178 HAECKEL, W Freie Wissenschaft und freie Lehre, 1908, Leipzig, pp 68-69
- 179 HUXLEY, T Evolution and ethics, and other essays, Collected Works, New York, 1894, ix, p 21
- 180 TILLE, A Von Darwin bis Nietzsche, 1895, Leipzig, p 120
- 181 MYERSON,^a p 294
- 182 EMERSON, HAVEN Epidemiology a possible resource in preventing mental disease, Mental Health, Publ of the Am Assoc Advancement of Science, no 9, Science Press, 1939, pp 9-13

MEDICAL AND SOCIAL FACTORS IN CRIME¹

By A. WARREN STEARNS, M.D., *Boston, Massachusetts*

WHEN a child is born his behavior is almost entirely on a physiological basis. He reacts to various stimuli on a reflex level and draws upon his heritage through past ages for motivation. In other words, his conduct is asocial. His parents begin the task of training forthwith, just as they would in the case of any other animal. This training at first has to do with the regulation of the various functions of the body and with teaching a certain amount of decorum. For a long time it has been recognized that children differ in their capacity to receive this sort of guidance. In some, tidy habits can be acquired in three months, in some six months or a year, and a few can never be taught correct habits. Obviously, the technique of the parent can be resolved to a very simple formula, the punishment of vice, and the reward of virtue.

Upon reaching the age of five or six the child is sent to school, his behavior is then dependent upon the thoroughness with which the previous parental duties have been carried out. Here a new factor comes in to direct the instinctive drives of the little animal. He is directed to a certain extent by teachers, but more important still is the social pressure which comes from his associates. They begin teaching him the ways of the world. Brutally and cruelly they ridicule or punish deviation from the customs current in any particular community. To be sure he learns to read and write and to add and subtract, but he also learns how to behave like the other children. Here again it has long been observed that there are individual differences in the ease with which this latter knowledge is acquired.

A few stormy years of adolescence, more or less hectic according to individual qualities, and he is embarked upon adult life. Here he has the task of conforming to the requirements which the adult population imposes upon him, and especially he must get a job, fit himself to his employment, and then get a wife, establish a home, and begin the same program which he has just completed, with another generation. He continues to develop and progress through mid-life. Then come the effects of the disintegrating process of later years, and finally he leaves life as he entered, entirely helpless. Such is the traditional trajectory of life.

Society in the main tends to approve and reward the conventional life. Just as parents direct the child through praise and blame, society controls the adult. The mechanism is identical. However, some do not conform and from the dawn of history we can trace the efforts of society to induce or compel conformity to a conventional pattern. In primitive society this is done ruthlessly. There are no laws, but there are mores and the non-conformist is hunted down and destroyed much as a skunk or snake is destroyed.

* Received for publication February 13, 1943

by civilized persons By common acclaim only, the non-conformist is destroyed

As we ascend the long hard climb through various stages we find a gradually developing attitude toward criminals While the savage governs his conduct by the pleasure or displeasure of the spirits, in early biblical days it was the purity of the city which was being sought Personal motivation in punishment has always been identical, but the assigned purpose has always been altruistic In the Roman days abstract justice became the goal and later the deterrent effect of punishment¹

This brings us up to relatively modern days To this point there has been little thought of individual differences, most legal philosophy having to do with the social damage and abstract theories of right and wrong During the great revolutionary period, punctuated by the French and American Revolutions, there was a great awakening in humanitarian fields Man could no longer see his neighbor drawn and quartered, or burned at the stake, and the so-called sanguinary laws of Europe were abolished in Massachusetts in 1786 The work of John Howard either caused a universal awakening or was the expression of such One of the immediate phases of John Howard's work was an interest in the sanitary conditions of prisons So unhealthy were they that the scourge of typhus fever was popularly called "jail fever" The bad smell of dirty, sick bodies was referred to as "prison odor" So Howard drew up plans for a penitentiary house with single cells where men could have a chance for penitence and prayer and be cured The first of these was erected in New York in 1798 In 1805 the Massachusetts State Prison was opened No greater idealism was ever expressed than that which gave rise to the Charlestown State Prison Benevolence and religion seemed to offer salvation from the scourge of crime Yet in a very few years it was found that all persons could not be cured by this method Those who had been once in the penitentiary tended to come again Almost for the first time individual differences were indirectly taken account of and in 1818 an habitual criminal law was passed

In 1816 an act for the relief of poor debtors was passed, thus recognizing the helplessness of this class In a general way the series of laws softening the punishment of debtors was opposed by the legal profession It was thought that if debtors were not punished that no one would pay his bills Here again, no allowance was made for individual differences We shortly enter an era in which education and training appear to be the answer to the problem of criminology In 1821² the House of Industry was established in Boston modeled after previous ones in Marblehead and Salem, and if one reads the report of the committee recommending this he finds that honest work and learning a trade are offered as cure-alls for this type of social ills In 1824, the House of Refuge was opened in New York and shortly after a similar one was opened in Massachusetts³ It was thought that the proper training of neglected children would furnish the key to the cure of crime and their published reports breathe great optimism as to the future

The Livingston Code begun in 1821 provided for the abolition of capital punishment and its spirit was remedial rather than vindictive. Already, in the appointment of physicians, a considerable beginning had been made toward remedying the sanitary condition of prisons.

Meantime the reformatory movement had grown to full stature having its origin with Admiral Macanochie in 1798.⁴ This gradually developed into the Irish system perfected by Sir Walter Crofton in Dublin. The American replica of the Irish system first appeared at the Elmira Reformatory. An excellent account of this is found in Wines.⁵ Here again a formula was offered for the cure of crime regardless of individual differences.

In 1875 the Massachusetts State Board of Health made its famous report of the sanitary conditions at the Charlestown State Prison showing that even at this relatively modern time rather inadequate provision had been made for the health of inmates. From then on medical services in prisons were improved and the medical component in the care of prisoners showed a rapid increase. Finally, some prisons were actually the healthiest places in the world.

There was gradually accumulated a vast store of knowledge throughout all this period of the relation between physical ill health and crime. Cripples, the blind, persons with tuberculosis and other chronic diseases, unable to compete on equal terms with their fellows, were found in prisons out of all proportion to their occurrence in society.

It is difficult to say when an interest in the mental state of prisoners began. Benjamin Rush⁶ in his celebrated book published in 1812 has a page or two on moral insanity followed immediately by a plea for more humane treatment of prisoners. In 1835 when the Worcester Lunatic Asylum was opened a great many of its early inmates were taken thence from prisons and the Fourth Annual Report of Dr. Samuel Woodward, Superintendent,⁷ gives a lurid account of their treatment in prison and the condition in which he found them. The report of Thomas Hazard in 1854 gives similar examples from Rhode Island. Gradually, the policy of removing the insane from prisons was definitely established, but there was a plague spot in the determination of sanity. One of the earliest expressions of this and one of the best is an account of an individual in a Dublin asylum which is quoted as follows:⁸

In the Richmond Lunatic Asylum, Dublin Mr. George Combe saw a patient in 1829, who has been confined for ten years. He exhibited a total want of moral feeling and principle, yet possessed considerable intelligence, ingenuity, and plausibility. He had been a scourge to his family from childhood—had been turned out of the army as an incorrigible villain—had attempted the life of a soldier—had been repeatedly flogged—had since attempted the life of his father. Respecting this man, Dr. Crawford, Substitute Physician at the Asylum, made the following remarks: 'He never was different from what he now is. He has never evinced the slightest mental incoherence on any one point, nor any kind of hallucination. It is one of those cases where there is great difficulty in drawing the line between extreme moral depravity and insanity, and in deciding at what point an individual should cease to be considered as

a responsible moral agent, and amenable to the laws. The governors and medical gentlemen of the Asylum have often had doubts whether they were justified in keeping him as a lunatic, thinking him a more fit subject for a Bridewell. He appears, however, so totally callous with regard to every moral wrong, so completely destitute of all sense of shame or remorse, when reprimanded for his vices or crimes, and has proved himself so utterly incorrigible throughout life, that it is almost certain that any jury, before whom he might be brought, would satisfy their doubts by returning him insane, which, in such a case, is the most humane line to pursue. He was dismissed several times from the asylum, and sent there for the last time for attempting to poison his father, and it seems fit he should be kept there for life as a moral lunatic but there has never been the least symptom of diseased action of the brain, which is the general concomitant of what is usually understood as insanity. This, I consider, might with propriety be made the foundation for a division of lunatics into two great classes,—those who were insane from original constitution, and never were otherwise, and those who have been insane at some period of life from diseased action of the brain, either permanent or intermittent.”

With the rapid development of hospitals for mental disease there grew up a specialty called psychiatry dealing at first with those gross mental disorders called insanity, but gradually coming to concern itself with behavior disorders of every nature. As early as 1905, Dr. Guy Fernald, a psychiatrist, was appointed physician to the Massachusetts State Reformatory at Concord and began a life of service in the interests of a scientific criminology. This was followed by similar appointments elsewhere, and elaborate systems of classification developed. This effort grew more and more complex, but, alas, cures were infrequent. It was recognized that a varying percentage of inmates were insane, and these were taken to hospitals for mental disease. It next appeared that a larger percentage were feeble-minded. An attempt to handle this group resulted in the passing of laws for the committing of defective delinquents, especially in such states as New York and Massachusetts. Then came the great schism over personality disorders. Some important persons believed that all gross vagaries of conduct were in themselves *prima facie* evidence of a certain degree of mental aberration, while others insisted upon gross evidence of psychopathy as a criterion. This question is still undecided and perhaps is no better stated today than it was by Sampson.⁹

The question of the mental status of prisoners in actual practice is largely an academic one except in the field of juvenile delinquency and in the case of particularly serious crimes. The great mills grind on. The courts in our large cities see hundreds and thousands of cases each year with little regard as to the mental condition of petty offenders.

Perhaps the greatest contribution of the psychiatrist has come through the fact that careful histories of offenders were taken which not only brought out the mental attributes of the individual offender, but also portrayed the environment from which he had sprung. This led to extensive research in the field of sociology by many of the leading sociologists of the country.

The writer has for many years regarded the vast majority of criminals as handicapped persons. Society has recognized three types of persons

needing public aid. These have been called the sick, the poor and the bad, and have led to the establishment of hospitals, poorhouses, and prisons for their care. All that we can say of these three groups is that certain individuals are preponderantly sick and therefore their illness is what calls for first attention. Others are preponderantly poor or bad. In the field of etiology their difficulties appear to spring from the same source. They all tend to be handicapped, each one with a large medical component. A most cursory scrutiny of the several types of institutions for these individuals shows that there is a tremendous overlapping. The relation between poverty and disease is a very definite one, although there is still a great deal of debate as to which is primary. This is a good deal like the proverbial debate as to which comes first, the hen or the egg. Obviously, there are certain persons who are physically ill and because of this handicap become impoverished and because of their impoverished condition are led to crime. Although it will be possible to fix the blame in individual cases, in general, crime, vice and disease are triplet sisters all springing from the same social sources. Needless to say the mental status of the individual is often very fundamental, and for this reason it may truthfully be said that basically crime is a social disorder. Mental disease, defect, or peculiarity is important in that social stress often bears hardest upon those who are least able to withstand its pressure. It seems helpful, however, to have some working classification of this very complicated and mixed social and medical problem. The following classification has served the writer's purpose in this matter.¹⁰

The Child As has been said above, the child is by nature a non-conformist. The law recognizes his helplessness in some ways until he is 21 years of age. He is entirely dependent upon the status of his parents and home and the task of being taught the ways of prudent conduct. Furthermore, many criminal careers begin during adolescence and it appears to be a phase through which they go. This is well expressed by Cabot in the introduction to Dr. Glueck's book.¹¹

The Aged Likewise the helplessness of old people is proverbial and yet, they are often obliged to lead a competitive life. For this reason their handicaps frequently lead to delinquency. Furthermore, there are factors in their sexual life which lead to difficulties.

Handicapped Classes There are many groups in our society against whom great odds are arrayed. Differences in race, sex and religion render the task of a conventional life more difficult for a substantial proportion of our population.

The Insane Nobody knows how many insane there are, but their clashes with the law are such that it is necessary to confine in Massachusetts about 1/150 of the population.¹²

The Feebleminded Certain children do not develop intellectually and are called feebleminded. It is estimated that about 2 per cent of the population should be so classified. We have just been through an age when the feebleminded have been pictured as peculiarly criminalistic and now their helplessness

ness seems to be a larger factor. They often come from feeble-minded families and so are neglected. Those needing the most training often get the least.

The Neurotic Although not specifically criminalistic, the handicap of the neurotic person is occasionally associated with crime.

The Disordered Personalities This group occupies a vague zone in the social hierarchy and is still ill-defined by the medical profession. It has to do with those persons who, through personal peculiarities, are unable to adjust and adapt themselves to the requirements of society, and so become social problems in one way or another. The morbidly contentious find it difficult to obtain employment. They are continually agitating, and nobody wants them. They are frequently found on relief, in prisons and even in hospitals for the insane. The inadequate personality often gives up without a struggle and is feebly resistant to alcohol, and the emotionally unstable are often incapable of sustained productive effort. This group not only forms an important component in definite social disorders, but makes up a large number of those who are found in clinics appearing on the surface as neurotic. Needless to say, many of these persons appear in the sedimentary stratum. Certain states have passed laws for the commitment of such individuals if their conduct is criminalistic.

Drug and Alcohol Addiction Addiction to habit-forming drugs including alcohol, has long been considered a medical problem, and, in the past, there have been many programs under medical stimulus and leadership attempting to attack this problem in an intelligent way. We have no census of alcoholic patients, but every index tends to show the load to be tremendous. There are approximately 84,863 arrests in Massachusetts every year for drunkenness. Thirty-two per cent of the patients admitted to the state hospitals are said to be intemperate. Alcoholism has been shown to be a very large component in the admissions to the Boston City Hospital. There is no more discouraging problem with which to deal than that of alcoholism. The police handle the same cases over and over again. Certain persons have literally hundreds of sentences to jails and houses of correction. At the present moment, although there has been very recently a vigorous attempt to promote attention to this group, there is no state-wide program for prevention or cure, nor is there an adequate meeting of the minds of police, welfare and medical authorities. Quite a bit of the beneficent effort to raise the level of living of certain of the dependent groups is almost entirely vitiated through diversion of relief from the home to the saloon. The drug problem is similar, but, of course, very much less flagrant. A surprising number of those who fail to meet their obligations in life are alcoholic and get into the sedimentary immobile stratum of society.

Physical Disease Wherever criminal populations have been studied by physicians there has been found to be an excess of physical disease or defect. There is often a direct relationship between the criminal career and ill health although it is often difficult to say which one stands in a causative relationship.

CONCLUSION

1 From the above it would appear that criminals are handicapped persons. We have at one end of the scale cases whose difficulties are entirely due to mental disease. At the other end are pure social problems with all possible gradations in between. I would not be bold enough to place a median.

2 It seems obvious that attempts of society to handle criminals as a class by a general rule of treatment applied to all has not worked satisfactorily in the past.

3 This leads to the hypothesis that the best way to handle the problem of crime is through individual study. In certain cases this calls for elaborate psychiatric investigation, in others for equally elaborate sociological study, but in the main all offenders should have preliminary social case work carried out, in order that the needs of the individual can be brought into focus and assigned to the proper persons for treatment and care.

4 Studies of prisoners at the present moment have not resulted in startling cures, but have furnished the basis upon which better social engineering can be done. The knowledge of the personality of criminals today is far in advance of the procedures by which they are handled in any society.

5 It is to be hoped, as knowledge accumulates, that in the course of time general laws can be discovered which will enable preventive measures to be carried out on a large scale. For instance, in medicine the discovery of the infectious nature of diarrhea in children has led to the control of milk supplies in our great cities and thus practically controlled this disease which once carried off a very large percentage of children during their first year. Unfortunately, at present very few such laws are known and we are still obliged to handle each case empirically, often almost on an instinctive level.

BIBLIOGRAPHY

- 1 STEARNS, A. WARREN. The evolution of punishment, Jr. *Crim. Law*, 1936, *LI*, 219-230.
- 2 QUINCY, JOSIAH. Report in regard to House of Industry, 1821.
- 3 House of Refuge, First Annual Report, 1826.
- 4 MACONOCHE, CAPTAIN ALEXANDER. Report.
- 5 WINES, FREDERICK H. Punishment and reformation, 1895, Crowell, New York, 192-228.
- 6 RUSH, BENJAMIN. Medical inquiries and observations upon the diseases of the mind, 1812, Philadelphia, p. 357.
- 7 WOODWARD, SAMUEL. Senate document No. 13—Fourth Annual Report of State Lunatic Asylum, 1836.
- 8 SAMPSON, M. B. Rationale of crime and its appropriate treatment, being a treatise on criminal jurisprudence considered in relation to cerebral organization, 2nd London edition, 1846, Appleton, New York.
- 9 Same as above.
- 10 STEARNS, A. WARREN. The personality of criminals, 1931, Beacon Press, Boston.
- 11 GLUECK, SHIRLEY. Five hundred criminal careers, 1930, Knopf, New York.
- 12 STEARNS, A. WARREN. The role of the physician in a competitive society, *New England Jr. Med.*, 1941, *CCLXIV*, 879-890.

PRIVILEGED COMMUNICATIONS: IS JUSTICE SERVED OR OBSTRUCTED BY CLOSING THE DOCTOR'S MOUTH ON THE WITNESS STAND? *

By ZECHARIAH CHAFEE, JR.,[†] *Cambridge, Massachusetts*

PHYSICIANS and surgeons are required by the ethics of their profession to preserve the secrets of their patients which have been communicated to them or learned from the inspection of symptoms and other bodily conditions. How far this ethical requirement should be enforced by law is a question on which there is much difference of opinion among both lawyers and doctors.

No state has made disclosure of confidence a crime, as it is in France, but in some the license to practice may be revoked for this cause. Seventeen states still seem to preserve the view of the English common law that there is no legal check upon the revelation of medical secrets. On the witness stand, at all events, a doctor in these states must tell all he knows.¹

The remaining states adopt a half-way attitude towards the obligation of secrecy, of which the New York statute (first enacted in 1828) is typical.² Unless the patient consents, the doctor is not allowed, while testifying in court, "to disclose any information which he acquired in attending a patient in a professional capacity and which was necessary to enable him to act in that capacity." Thus there is no liability to the patient if the doctor tells every last detail in clubroom gossip or the thickly veiled items of a medical journal, but he is prohibited from divulging any of the truth in the place where it is most needed and usually most stringently required—the witness stand.

Some of these statutes make exceptions for special medical situations, such as abortion, in which disclosure is badly needed.³ Several of the states,

* Received for publication January 25, 1943.

Some of this paper has previously appeared in 25 *Rhode Island Medical Journal* 157-163 (July, 1942). The author has been greatly aided by the classic discussion in 8 *Wigmore on Evidence* (3d ed 1940) §§ 2380-2391. See also 152 *Law Times* 53 (1921), debates at British Medical Association, 153 *Law Times* 228, 252 (1922), debates at British Medical-Legal Society, 83 *Law Journal* 320 (1937), debates in House of Commons.

[†] Professor of Law, Harvard Law School.

¹ These states are Alabama, Connecticut, Delaware, Florida, Georgia, Illinois, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, Rhode Island, South Carolina, Tennessee, Texas, Vermont, and Virginia.

² N. Y. Civil Practice Act (1920) §§ 352, 354, as subsequently amended. See 3 *Gilbert-Bliss, Civil Practice of New York Annotated* (1926), §§ 352, 354, and (1941) Cumulative Supplement to same.

³ *Wigmore*, § 2380, n. 5, gives full references to the statutes in the following states. The ensuing list mentions only the date of the original enactment as given by *Wigmore*, without regard to subsequent amendments. The statutes vary in their terms, particularly as to waiver of the privilege. The ensuing list mentions only variations of especial medical interest, including the fact of adoption of the Uniform Narcotic Drug Act (UNDA). Alaska (1913) (except for insanity), Arizona (1913) (UNDA), Arkansas (1919), California (1872) (except for mental condition and venereal disease); Canal Zone (1934), Colorado (1921), Columbia (Dist.) (1919) (UNDA), Hawaii (1925) (UNDA), Idaho (1919),

recognizing the doctor-patient privilege in general, have adopted the Uniform Narcotic Drug Act, which provides

"Information communicated to a physician in an effort unlawfully to procure a narcotic drug, or unlawfully to procure the administration of any such drug, shall not be deemed a privileged communication" ⁴

The general policy of the law is to obtain as many facts as possible about a controversy on trial, but this policy is cut into at many points by what are called rules of evidence. For instance, a witness cannot tell what he has learned from hearsay and not from his own observation, because such testimony is likely to be untrustworthy. The physician's evidence would be free from this objection, but the law often keeps out reliable testimony if it was acquired by the witness through some confidential relation. Thus a husband would hesitate to tell his wife about damaging facts and the thorough intimacy of marriage would be turned into watchful suspicion and reticence, if the law did not refuse to make her the means of his undoing ⁵. Likewise a man might not consult an honest lawyer, or if he did, would tend to keep back from him anything that looked unfavorable to the case, if the lawyer could be made the leading witness against him and forced to reveal all that was told him by his client. So the lawyer cannot speak without his client's consent ⁶. In many states a statute protects the secrets of the confessional ⁷, and even without such legislation few lawyers would have the hardihood to ask that a priest who keeps silent be imprisoned for contempt of court.

Some doctors may feel that it is an unfair discrimination against their profession if lawyers' secrets are protected from disclosure in court and yet physicians' secrets must be laid bare. What is sauce for the goose ought to be sauce for the gander. Yet one could turn this argument for equal treatment the other way round, and deny protection in both cases. Perhaps lawyers like doctors should be forced to divulge information when the judge thinks disclosure essential to the public interest. Jeremy Bentham became white-hot against the inviolable secrecy of communications between attorney

Indiana (1926), Iowa (1897) (UNDA), Kansas (1923), Kentucky (1915), Louisiana (1928), Michigan (1915) (except for illegal marriage of persons sexually diseased), Minnesota (1913) (except for bastardy), Mississippi (1906), Missouri (1919) (except for abortion), Montana (1935) (UNDA), Nebraska (1922) (UNDA), Nevada (1912) (UNDA), New Mexico (1929) (UNDA), New York (1928) (except for narcotic investigations), North Carolina (1919) (allows presiding judge of superior court to compel disclosure when necessary to administration of justice, UNDA), North Dakota (1913), Ohio (1921) (UNDA), Oklahoma (1931) (UNDA), Oregon (1920) (UNDA), Pennsylvania (1895), Philippine Islands (1901), Porto Rico (1911) (except for malpractice, UNDA), South Dakota (1919) (UNDA), Utah (1917) (UNDA), Virgin Islands (1920), Washington (1909), West Virginia (1897) (UNDA), Wisconsin (1919) (except for lunacy and malpractice, UNDA), Wyoming (1920) (UNDA).

⁴ Uniform Narcotic Drug Act § 17, paragraph 2. This statute has been adopted in the following states and territories, of which those starred in the list do not recognize a general doctor-patient privilege: Ariz, DC, Haw, Ia, Md*, Mont, Neb, Nev, NM, NC, Oh, Okla, Ore, PR, SC*, SD, Tenn*, Tex*, Ut, W Va, Wis, Wyo.

⁵ See Wigmore, §§ 2332-2341.

⁶ See Wigmore, §§ 2290-2329. He gives full arguments for and against this privilege in § 2291.

⁷ See Wigmore, §§ 2394-2396.

and client "Whence all this dread of the truth? Whence comes it that any one loves darkness better than light, except it be that his deeds are evil?"

Proposals are now under consideration for extensive modifications of the attorney-and-client privilege, as Professor Edmund M. Morgan shows elsewhere.⁸ However, the success or failure of these proposals ought not to affect the question whether medical secrets should be inviolable in court. The relation between lawyer and client does differ materially from the relation between doctor and patient, as I shall explain in the next paragraph. Each privilege should be judged on its own merits regardless of the fate of some other privilege. The administration of justice ought not to be shaped by interprofessional jealousies and trivial claims to prestige. Instead, we can all agree that it is a misfortune when a lawsuit is won by the party who would lose it if all the facts were known, and that we increase the risk of such a miscarriage of justice whenever we allow an important witness to keep any helpful facts away from the judge and jury. Very strong reasons should be required to justify any rule of law which keeps truth firmly concealed. Secrecy in court is *prima facie* calamitous, and it is permissible only when we are very sure that frankness will do more harm than good. With doctors' secrets as with any other kind of secrets, the only proper test is the welfare of the community. Does courtroom secrecy in the particular case produce a public good which more than offsets the risks resulting from the concealment of truth and from the lies which can be made with less fear of detection? There is no profession with a higher sense of public welfare than the doctors', therefore, if the doctor-and-patient privilege is socially undesirable, they should be among the first to oppose it. Then they should urge its abolition wherever it exists, and object to new legislation extending it.

The reasons usually advanced for extending the privilege of silence to the medical profession are not wholly satisfactory. First, it is said that if the patient knows that his confidences may be divulged in future litigation he will hesitate in many cases to get needed medical aid. But although the man who consults a lawyer usually has litigation in mind, men go very rarely to a doctor with any such thought. And even if they did, medical treatment is so valuable that few would lose it to prevent facts from coming to light in court. Indeed, it may be doubted whether, except for a small range of disgraceful or peculiarly private matters, patients worry much about having a doctor keep their private affairs concealed from the world. Usually the patients themselves bore their casual acquaintances with full details of an operation or a disease. This whole argument that the privilege is necessary to induce persons to see a doctor sounds like a philosopher's speculation on how men may logically be expected to behave rather than the results of observation of the way men actually behave. Not a single New England state allows the doctor to keep silent on the witness stand. Is there any evidence

⁸ Morgan, "Suggested Remedy for Obstructions to Expert Testimony by Rules of Evidence," (April 1943) 2 Clinics 1627, (April 1943) 20 U of Chi L. Rev.

that any ill or injured person in New England has ever stayed away from a doctor's office on that account?

The same *a priori* quality vitiates a second argument of the framers of the New York statute about the evils of compelling medical testimony "During the struggle between legal duty on the one hand and professional honor on the other, the latter, aided by a strong sense of the injustice and inhumanity of the rule, will in most cases furnish a temptation to the perversion or concealment of the truth, too strong for human resistance" Has any member of the numerous medical societies in New England observed such a tendency among New England doctors to commit perjury for the sake of "professional honor"?

There is far more danger of perjury if the physician cannot testify, only it will be perjury by the patient In many states where the privilege exists, an unscrupulous plaintiff in an accident case can exaggerate the injury without fear of contradiction by the doctor whom he consulted right after the accident The patient can tell the sad story of his injuries to judge, jury, and spectators, and then he can object that it would violate his bodily privacy if the doctor were allowed to take the stand and testify that the accident had left no traces one hour after it occurred Fortunately, there is some limit to this absurdity Most courts hold that if the patient goes into the details of his injuries, then he has waived his privilege, he has thrown open the whole question of his bodily conditions⁹ Otherwise he could make the statute both a sword and a shield

Yet this rule about waiver does not promote truth-telling any too well The patient may tell some rather big lies about his health without "going into details," and the courts are by no means clear in defining the point where details begin There is also abundant confusion on the question whether what the patient says under cross-examination opens the door for his doctor to testify Some courts hold that cross-examination is not a waiver like direct testimony, because the patient does not now speak willingly By this view, the opposing lawyer who ventures to ask the patient any questions may find the witness going into the most intimate details without regard to either privacy or truth, and yet the lawyer will be helpless to contradict this highly colored story by calling the physician

The absurdity of this solicitude for the patient's privacy is illustrated by a recent Ohio case¹⁰ The plaintiff sued the owner of a building for heavy damages, charging that the defendant negligently suspended a fire hose from the building in such a manner that a violent wind caused the hose to break a window, knocking glass against the plaintiff He testified that since this accident he had suffered loss of weight, severe and chronic headaches, failing eyesight, insomnia, facial paralysis, and inability to walk normally, but that

⁹ The cases are collected in 114 American Law Reports Annotated 708 (1938) (This series will be hereafter cited as A L R) See also Wigmore, § 2380
¹⁰ *Harpman v. Deane*, 133 Oh St 1, 10 N E (2d) 776 (1937), discussed in 11 L. Cinc L. Rev 544

before the glass hit him his general condition was "very good" On cross-examination he admitted that he had consulted various physicians before the accident The defendant called one of these doctors for the purpose of showing that the plaintiff was suffering from anemia before the accident The court refused to allow the doctor's evidence "in view of the very delicate and confidential nature of the relation "

Another argument for the privilege is that employees are often treated after accidents by physicians who are in charge of the company hospital or otherwise dependent upon the good will of the employing corporation It was urged to legislatures that some of these physicians were taking advantage of their position to obtain from the patients information which would tend to defeat a claim for damages This argument has the merit of not being abstract, but of asserting a basis in fact Even if true, it might be wiser to admit the evidence of the physicians, trusting in the jury to discount it heavily if an improper attitude towards the patient exists

Where the statutory privilege is in force, what is its scope? In the first place, what sort of medical person is included? ¹¹ Any licensed physician or surgeon falls within the statute, and this applies to hospital physicians though they are not specifically selected by the patient ¹² There is no privilege for communications to unlicensed practitioners Thus mental healers, chiropractors and osteopaths can be forced to disclose communications from their patients, unless perhaps their professional status is expressly recognized by law How about the numerous assistants who surround doctors under modern conditions? Many attempts have been made to prevent nurses from telling about their patients, but these have usually failed ¹³ Most courts say that if public policy demands the extension of the privilege to nurses and other hospital attendants, then the change in the law should be made by the legislature, not by judicial action Here is an enticing invitation to organizations of nurses to increase their professional prestige by lobbying for a statutory amendment which will put them on the same high level of secrecy as doctors This result has already been accomplished in New York and a few other states Dentists may also resent being left out in the cold with druggists And the privilege does not apply to an unlicensed "orthopedist" who is teaching gymnastic exercises taken by medical advice ¹⁴ Those psychoanalysts who have been too busy to study medicine must have spicier facts to relate than physicians, but no court has yet bound them to secrecy The status of veterinarians was raised in an Iowa suit brought by the owner of a race horse against the Western Union for delay in transmitting a telegram, "Bravo is sick, come at once" The doctor arrived at last, but Bravo died The Western Union lawyer asked the doctor what the owner said to him about Bravo's symptoms The owner urged that

¹¹ The cases are collected in 68 A L R 176 (1930), Wignmore, § 2382

¹² The cases are collected in 22 A L R 1217 (1923), 72 U S Law Rev 619 (1938)

¹³ The cases are collected in 39 A L R 1421 (1925), 68 A L R 177 (1930) On hospital attendants, see 22 Marquette L Rev 211 (1938)

¹⁴ *Laurie Co v McCullough*, 174 Ind 477, 19 N E 1014 (1909)

the communications from Bravo to the veterinary were privileged, but the court held that veterinarians were not covered by the statute¹⁵

No end of trouble has arisen about the admissibility of medical records. If a doctor cannot tell the court what he saw, then the hospital records in which he wrote down what he saw seem logically just as unavailable. Yet some courts are impressed by the fact that the law requires such records to be kept, and see little sense in this if they cannot be used for the sake of attaining justice¹⁶. For example, it would be absurd if the records of a state hospital for the insane could not be consulted in a will contest for their bearing on the mental capacity of the testator¹⁷. So judges have been inclined to read a wide exception into the statute to cover such situations. Thus death certificates ought to be admissible¹⁸. In New York this exception has been extended to public health records, which were admitted to show that the defendant was a typhoid carrier who had been warned not to participate in the service of food. The records were used to establish her liability in damages to the estate of a man who died of typhoid after eating food which had passed through her hands¹⁹.

How about autopsies? It is generally held that if the doctor had not attended the person during his lifetime, then the doctor can testify about performing an autopsy because the relation of the physician and patient did not exist²⁰. "A deceased body is not a patient"²¹. For example, a man who carried heavy accident insurance became suddenly ill. The physician who was called removed him to a hospital and there continued to treat him until his death. The hospital pathologist was then summoned to perform an autopsy, which showed that the man died from the effect of wood alcohol in home-made gin. The first doctor was allowed merely to give his opinion that wood alcohol in gin was capable of causing the death, but the second doctor was permitted to give all the details discovered during the autopsy²². However, another court regarded this device of getting away from the privilege by switching doctors as an arrant subterfuge and ruled out the autopsy by asking

"Can a hospital, immediately after the death of one of its patients, discharge the physician who had attended the patient up to the time of death and thereafter rush the dead body to the morgue, and direct the physician at the head of the pathological department to perform an autopsy, and thus evade the statute which sealed the lips of the first physicians? We think these questions should be answered in the negative, and that a physician

¹⁵ *Hendershot v Western Union Telegram Co*, 106 Iowa 529, 76 N.W. 828 (1898).

¹⁶ The cases are collected in 75 A.L.R. 393 (1931), 120 A.L.R. 1140 (1939).

¹⁷ *Liske v Liske*, 135 N.Y. Supp. 176 (1912).

¹⁸ Yet some courts exclude them. See the authorities in Wigmore, § 2385a, 17 A.L.R. 370 (1922), 42 A.L.R. 1455 (1925), 96 A.L.R. 341 (1935).

¹⁹ *Thomas v Morris*, 286 N.Y. 266, 36 N.E. (2d) 141 (1941), annotated in 136 A.L.R. 856.

²⁰ The cases are collected in 58 A.L.R. 1134 (1929), 35 Law Notes (N.Y.) 87 (1931).

²¹ See case cited in note 22 *infra*.

²² *Trazichs' Ins Co v Bergeron*, 25 F. (2d) 680 (C.C.A. 8th, 1928).

under such circumstances steps into the shoes of the attending physician, and must be treated as if he were the assistant of the attending physician, holding the autopsy at the direction of the latter, and that the information acquired by him through the autopsy is privileged " ²³

The question what part of the physician's knowledge about the patient is non-professional raises great difficulties. The fact that he was ill, the number of visits made, the performance of an operation at a certain date may be disclosed, but not the nature of the illness or the operation. It would seem that symptoms which were obvious to every one without medical inspection cannot be said to be disclosed in confidence, but several cases have forbidden hospital doctors to testify that when a man was brought in they smelled liquor on his breath or observed other common symptoms of intoxication ²⁴

The information must be received in a professional relation, not everything medical which a doctor sees or hears is privileged. For example, if called to a house to see a person, the doctor can sometimes tell what he incidentally observed as to the health of other members of the family ²⁵. If the patient voluntarily employed the physician, the privilege is clear. But suppose the doctor renders first aid to an unconscious man. No confidence is reposed, but the doctor does attend him in "a professional capacity". In a New York case a physician was called by a hotel to attend a guest without the latter's knowledge. The man said he had taken poison, but cursed the doctor and refused to have anything to do with him. The doctor administered a hypodermic. The hotel guest was held to be a patient, although he did not want to be, and the doctor was forbidden to tell about the poison in order to show that the patient had forfeited his life insurance by committing suicide ²⁶.

Even though a professional relation exists, only information necessary to enable the doctor to act in that capacity is privileged. Matters which are entirely distinct from medical facts may be disclosed, ²⁷ for instance, the patient's remarks about his will. An Indiana doctor was called to attend a sick wife and also cast a professional eye on her husband. While leaving the house, he heard the husband say "I will get her yet, damn her, I will get her yet". Shortly afterwards the wife shot her husband. When tried for murder, she called the doctor as a witness to support her story that she killed her husband in self-defense while he was approaching her with an open knife in his hand. The trial court excluded the doctor's evidence on the ground that he was in the house in the capacity of a physician. The jury disbelieved the wife's story and she was convicted of manslaughter. The

²³ *Matthews v Rev Health and Ins Co*, 86 Ind. App 335, 157 N E 467 (1927)

²⁴ The cases are collected in 79 A L R 1131 (1932)

²⁵ *Jennings v Supreme Council*, 81 N Y App Div 76, 81 N Y Supp 90 (1903). See *Nichols v State*, 109 Neb 335, 191 N W 333 (1922)

²⁶ *Meyer v Knights of Pythias*, 178 N Y 63, 70 N E 111 (1904)

²⁷ The cases are collected in 24 A L R 1202 (1923), *Wigmore*, § 2383, 13 Wash L Rev 141 (1938)

upper court reversed, holding that the doctor should have been allowed to testify about threats of death though not about health ²⁸

Often the illness and another fact are closely connected, as in a New York divorce trial which received much attention in the press 20 years ago, in which a physician was asked to disclose a communication from the misguided wife as to the paternity of an expected child. The referee excluded this communication, because it must have been given as a sequel to the wife's disclosure of her pregnancy, which was clearly privileged and could not be repeated. On the other hand, a California doctor was allowed to testify that while he was delivering an illegitimate child a certain man was present and admitted that he was the father ²⁹. A similar problem arises when the victim of an accident in describing his symptoms to a physician throws in occasional statements about the way he was hurt. Of course, the speed of the trolley car which hit him and the fact that he himself was not looking as he crossed the street are not really necessary for the application of surgical dressings, and the legitimacy of an expected child has no bearing on the medicines or other pre-natal care which should be given to the mother. (If the doctor were a psychiatrist, who was curing her of melancholia or some other mental or nervous disorder, questions on such a fact would be highly important.)

Logically, it may be that the facts leading up to a physical condition are often not "necessary to enable the physician to act in a professional capacity" and consequently are not protected by the statute. Yet practically it is very unjust to a patient, consulting a physician in a state where the law insists that the utmost confidence shall be preserved, if his conversations with the physician can be sifted out by the law into two classes of utterances and only one class is kept secret. Here comes a sentence which is held necessary for treatment, but the next, dealing only with the cause of the ailment, receives no protection. The dividing line may fall in the middle of a sentence. What sort of confidence is secured by the statute if a sick and perhaps hysterical patient must be constantly on the alert, every time a question is asked him, to determine at his peril whether it is necessary for treatment, and, even if it is, must be watchful lest he add something to his answer which is not necessary? If the privilege is to exist at all, the law might well take the position that all the communications of the patient which are actuated by his feeling of confidence in his medical adviser and which he would naturally make in furnishing the doctor with information as a basis of treatment are entitled to secrecy, even though some of these facts if wrenched from the conversation and taken singly have no medical value. A patient should not be forced to tell his story to the doctor with the circumspection of a lawyer drawing pleadings.

The privilege belongs to the patient and not to the physician. Hence the patient cannot be forced to testify about the consultation any more than the

²⁸ *Wier v. State* 192 Ind. 542, 137 N.E. 547 (1922)
²⁹ *Baird's Estate* 173 Cal. 617, 160 Pac. 1078 (1916)

doctor Conversely, if the patient consents to the disclosure, the doctor can no longer insist on remaining silent Is anything less than express consent enough? The effect of the patient's testifying about his own health has already been discussed Suppose the plaintiff in a personal injury case, who has been to several doctors, calls only one physician who is favorable to his own claim, can the plaintiff still insist that it might cause him "embarrassment and disgrace" if the defense were allowed to put on his other doctors who are ready to tell a very different story about the plaintiff's bodily condition? As to this the cases are in great confusion ⁸⁰

Sometimes the patient is dead and can no longer waive his privilege Must the doctor's lips then be sealed forever? Some statutes have neglected to provide for this emergency, whereas others expressly permit the executor or administrator of the patient to authorize the doctor to speak ⁸¹ Yet no matter how carefully the statute be drawn, it is likely to fail to specify some person connected with the decedent who has an excellent reason for desiring the doctor's testimony For example, in a Wisconsin case a widow suing as a beneficiary under an accident insurance policy was unable to prove that her husband's death was accidental except by the testimony of the physician who attended him The Wisconsin statute did not say that a beneficiary could waive the privilege Hence the court forced the doctor to keep silent, and the widow recovered nothing on the policy ⁸² Here the privilege, which is supposed to exist for the patient's benefit, operated to defeat one of his dearest desires Wigmore's view that nobody except the patient may take advantage of the privilege would have accomplished a just result in this case Certainly a person directly antagonistic to the patient should not profit from the privilege Many insurance policies endeavor to avoid such difficulties by a clause in which the insured waives the privilege in advance Such a clause is usually held valid, but it has no effect in New York ⁸³

The possibility that the patient's death silences the doctor is particularly objectionable when the patient was murdered It may be very important to have a physician disclose the physical condition of the victim during the interval between the crime and the death Sometimes a man kills a woman to get her out of the way because she is expecting a child and medical testimony is necessary to establish his motive Judges usually get around this difficulty by saying that criminal cases are not within the spirit of the statute, although some courts refuse to carve out such an exception ⁸⁴ Usually the desired testimony relates to the bodily condition of the victim, but it may conceivably concern that of the accused and here the bars have been higher ⁸⁵

⁸⁰ 62 A L R 680 (1929), 90 A L R 646 (1934), 51 Harv L Rev 1931 (1938), 31 Yale L J 529 (1922)

⁸¹ The cases are collected in 31 A L R 167 (1924), 126 A L R 380 (1940), Wigmore, § 2391

⁸² *Mame v Maryland Casualty Co*, 172 Wis 350, 178 NW 749 (1920) two judges dissenting, annotated in 15 A L R 1544

⁸³ The cases are collected in 54 A L R 412 (1928), Wigmore, § 7a

⁸⁴ The cases are collected in 45 A L R 1357 (1926); Wigmore, § 2385

⁸⁵ *People v Murphy*, 101 N Y 126, 4 NE 326 (1885)

Suppose a murder on a dark street. A policeman testifies that he could not recognize the killer, but that he shot at him as he was running away and winged him in the left arm. The prosecution calls a physician for the purpose of having him testify that one hour after the murder the accused called at his office and was treated for a bullet-wound in his left arm. The accused objects on the ground that he does not want to lay his ailments bare to the public. It is by no means certain on the authorities that the doctor would be allowed to testify, and so the prisoner might be acquitted for inability to identify him with the murderer.

A similar but much more perplexing conflict of loyalties was presented to Dr. C. E. May of Minnesota. While Dillinger, the former Public Enemy No. 1, was fleeing from prison, he went to Dr. May to be treated for gunshot wounds incurred during his escape. Was Dr. May ethically bound as a physician to preserve secrecy or was he under a duty as a citizen to notify the police? In fact he neglected to inform the police of his ministrations and was consequently imprisoned two years for harboring a fugitive wanted under a federal warrant.³⁶ *The Lancet* commented that "colleagues in every country will applaud his action in not betraying a professional trust."³⁷ Not many laymen are likely to join in the applause.

The Code of Evidence recently published by the American Law Institute, which Professor Edmund M. Morgan discusses elsewhere,³⁸ was originally drawn without any privilege for medical secrets in court.³⁹ At the last minute lawyers from states which have the privilege in their statutes forced the draftsmen of the Code to insert three new sections (§§ 221-223) establishing the physician-patient privilege. Fortunately, numerous limitations are specified which will prevent a repetition of many of the miscarriages of justice which I have already described. It may be argued in defense of the Code that these limitations greatly improve the law in states where the privilege now exists, and that they cut it down to so little that it will do no harm. Nevertheless, the American Law Institute might better have followed Hamlet's advice to the players, "O reform it altogether." In the first place, no matter how numerous and careful the limitations, some new situation is bound to arise in which secrecy ought not to be maintained, and yet the Code will prevent disclosure because the draftsmen in 1942 could not foresee this situation and so failed to insert any limitation to take care of it. Secondly, although the Code will make the law better in states which now have the privilege, it will make the law worse in states which have hitherto let in the truth. The powerful influence of the American Law Institute is likely in time to cause the general adoption of the Code in all the states, including those which now reject the doctor-patient privilege without apparently suf-

³⁶ 32 Mich. L. Rev. 1164 (1934).

³⁷ 226 Lancet 1183 (June 2, 1934).

³⁸ Morgan, "Suggested Remedy for Obstructions to Expert Testimony by Rules of Evidence," (April 1943) 2 Clinics 1627, (April 1943) 20 U. of Chi. L. Rev.

³⁹ See Proposed Final Draft (March 16, 1942, submitted to the Annual Meeting, May, 1942).

fering any consequent lack of medical care. Thus truth will be curtailed in regions where it is now available to make lawsuits end justly. And for what corresponding gain? In Massachusetts, for instance, the doctor is now protected by the trial judge against needless disclosures and told to speak out when truth is important. If Massachusetts should enact the Code of Evidence, many hours and many dollars will be spent on the intricacies of this new privilege,⁴⁰ and sooner or later some badly needed testimony will be lost but what will health gain? Does anybody seriously believe that the Massachusetts General Hospital or the Boston Lying-in or the Back Bay doctors will suddenly rise to new heights of excellence because now patients can throng to them assured that if they ever get into litigation a few of their medical secrets will occasionally be hidden from the prying curiosity of judges and jurors?

Legislatures and courts have been occupied for over a century in closing the physician's mouth in the very place where the truth is badly needed. And yet the much more important obligation of his silence in private life has hardly been considered by the law at all. We have put our money on the wrong horse. In the few instances in which honest patients do dread disclosure of their physical condition by a doctor, their fear is not that the truth may some day be forced from him in court, but that he may voluntarily spread the facts among his friends and theirs in conversation, and against this really dangerous possibility the statutes give almost no protection. The first and only decision on the doctor's liability to pay damages to his patient for a breach of confidence was made in 1920, under the common law, and recovery was denied, although a possible liability under different circumstances was suggested by the Nebraska court.⁴¹

A guest of a small hotel in a Nebraska town consulted a doctor who diagnosed his ailment as syphilis. He told the patient of the danger of communication and got his promise to leave the hotel the next day. On that day the doctor made a professional call on the owner of the hotel, and on finding that the patient had not moved out he warned the owner that the man had "a contagious disease." The patient was forced to leave the hotel, and sued the doctor for disclosing medical secrets.

Before discussing this unusual cause of action, let us see what would have happened if the patient had instead sued for slander. Since the diagnosis was perhaps incorrect the doctor might have been liable for slander, because of the defamatory nature of his statement. Yet the doctor might have raised the defense that there is no duty to pay damages for a slanderous statement if it is made honestly and on reasonable grounds in pursuance

⁴⁰ The New York doctor-patient statute (C.P.A. § 352) is eight lines long, and it takes six pages of small type just to summarize briefly the judicial decisions interpreting these eight lines. 3 Gilbert-Bliss, *Civil Practice of New York Ann* (1926) pp 281-285, and 1941 Cumulative Supplement to same, pp 192-194. The summaries of medical cases under § 354 occupy at least two pages more.

⁴¹ *Simonsen v Swenson*, 104 Neb 224, 177 NW 831 (1920), annotated in 9 A L R 1254, 20 Col L Rev 890, 34 Harv L Rev 312, 30 Yale L J 289, 75 J Am Med Assn 1207. See also *Smith v Driscoll*, 94 Wash 441, 162 Pac 572 (1917).

of a duty For example, if a doctor is required by law to report certain diseases to the Board of Health and makes such a report honestly but mistakenly, he is not liable for slander But should he be protected if he volunteers false statements to a private person? Suppose, on the other hand, that the doctor's diagnosis was correct, so that he told the truth to the hotel-keeper Then he would not be liable for slander, since truth is a defense in that kind of suit

But the actual suit was not for slander, it was for violation of the physician's contractual obligation to remain silent about his patient Can the truth be told with impunity if a confidential relation is thereby violated? The Nebraska court thought that a doctor ought to pay damages for telling the truth in breach of his duty to his patient, but that he should have the same right as a man who is sued for slander to insist that he acted under a duty to make the disclosure, which was more important than the duty to keep silent Clearly his statutory obligation to make health reports would justify breaches of confidence therein Here, however, he was under no legal obligation to divulge his patient's disease, but the court decided that in view of the great danger to life resulting from silence he had a moral obligation to speak which overrode his duty of secrecy Consequently, the patient lost his case

Much can be said for and against this result One commentator says that the Nebraska case "stands for the triumph of medical altruism over legal duty" Certainly, disclosure of risks of infection is very desirable, but it would be wiser to require all contagious diseases to be reported to a public official, who should have power to take all steps necessary to protect people from the patient, whether this required publicity or his removal to a hospital There are obvious dangers in leaving it to every physician to determine whether circumstances justify him in betraying intimate confidences

In conclusion, the law would seem to have directed its attention to the wrong quarter in laying so much emphasis on silence in the court and neglecting until now the patient's rights against disclosures to the world in general

CONTRACTS NOT TO PRACTICE MEDICINE ~

By E. MERRICK DODD,† *Cambridge, Massachusetts*

INTRODUCTION

A PHYSICIAN who has been practicing successfully in a certain small city and whose patients include residents of the city and of the neighboring countryside, sells his practice to a younger man and agrees that he will not thereafter practice medicine within a 25 mile radius of his former office.

A dentist with a similar established practice hires a younger dentist as his assistant and the latter agrees that if he ever leaves the former's employ he will not practice dentistry within a 10 mile radius.

The doctor who sold his practice, expecting to live thereafter on the proceeds of the sale, finds those proceeds inadequate and resumes practice in the same city in violation of his promise. The young dentist, after making an unsuccessful attempt to practice in some other city where he is unknown, returns to the city in which his former employer is practicing and opens an office there in violation of his promise.

I presume that most doctors and dentists would be surprised to learn that either of these supposed cases presents any problem for the lawyer. The contracts have been broken, what problem can there be for the law except that of finding the most effective means of giving the injured party an adequate remedy for the wrong that he has suffered? But the matter, as we lawyers know, is not quite so simple as that, for we must reckon with a long established and still vigorous doctrine of the common law—the doctrine that contracts in unreasonable restraint of trade will not be enforced by the courts.

It is probably safe to assume that when the average educated American who is not a lawyer reads the words "contracts in restraint of trade" there comes to his mind a picture of a great industrial combination which is seeking by means of restrictive agreements to obtain a monopoly in some line of business enterprise. The words will cause him to think of the Sherman Anti-trust Act and of dramatic struggles by Assistant Attorney General Thurman Arnold and his aides against a battery of corporation lawyers. If such a reader thinks of the medical profession at all he will think of the recent conviction of the American Medical Association for engaging in a conspiracy in restraint of the trade of Group Health, Inc.¹ He will be unlikely to see any connection between restraint of trade as he conceives it and the contracts to which we have referred.

"Contract in restraint of trade" is not, however, a phrase invented by a nineteenth century Congress as a method of curbing the growth of monopolistic business combinations. It is a phrase which has been used by com-

* Received for publication January 25, 1943.

† Professor of Law, Harvard Law School.

¹ *American Medical Association v. United States*, 63 Sup. Ct. 326 (1943).

on law lawyers for centuries—a phrase which was already old when the Court of Kings Bench dealt with the legality of such contracts at length in the case of *Mitchel v Reynolds*,² decided in 1711

The general principle announced in that case is as follows

"In all restraints of trade, where nothing more appears, the law presumes them bad, but if the circumstances are set forth, that presumption is excluded, and the Court is to judge of those circumstances, and determine accordingly, and if upon them it appears to be a just and honest contract, it ought to be maintained "

The court stated its objections to contracts which attempt to impose drastic restrictions on the contracting party's right to continue in business as follows

"The true reasons of the distinction upon which the judgments in these cases of voluntary restraints are founded, are, first, the mischief which may arise from them, 1st, to the party, by the loss of his livelihood, and the subsistence of his family, 2d to the publick, by depriving it of an useful member

"Another reason is, the great abuses these voluntary restraints are liable to, as for instance, from corporations, who are perpetually labouring for exclusive advantages in trade, and to reduce it into as few hands as possible, as likewise from masters, who are apt to give their apprentices much vexation on this account, and to use many indirect practices to procure such bonds from them, lest they should prejudice them in their custom, when they come to set up for themselves

"3dly, because in a great many instances, they can be of no use to the obligee, which holds in all cases of general restraint throughout England, for what does it signify to a tradesman in London, what another does at Newcastle? and surely it would be unreasonable to fix a certain loss on one side, without any benefit to the other " 3

The general principles enunciated in *Mitchel v Reynolds* have remained substantially unchanged after more than two centuries, although judicial notions of when a contract in restraint of trade is a "just and honest contract" (or is "reasonable" to use the more modern phraseology) have been modified somewhat to suit changing conditions and changing conceptions of economic and social policy

Contracts by the Seller of a Practice Not to Compete with the Buyer a Validity Long before the courts were called upon to consider contracts for the sale of a medical practice, they had established certain rules with respect to contracts for the sale of a business Even prior to the case of *Mitchel v Reynolds* it had been held that a contract by the seller of a business not to compete with the buyer in a limited area was valid 4 An agreement between

² 1 P Wms 181 (1711)

³ 1 P Wms 181, 190 (1711)

⁴ *Rogers v Parry* (1614) 2 Bulst 136 It is not mere antiquarianism which leads lawyers to cite seventeenth century cases in twentieth century articles The common law of today is affected by early precedents in a manner which has no parallel in medicine.

one who is selling his business and the purchaser that the former will not compete with the latter has obvious advantages for the buyer. If the business is to be carried on by him at the old place and under the old trade name, he will reasonably expect that many of the seller's former customers will transfer their custom to him. That expectation would be seriously impaired if the seller were free to compete and to urge his former customers to continue to trade with the same man rather than to continue to trade at the same store.

It is equally clear that the seller will ordinarily be able to obtain a better price for his business if, by making a legally binding agreement not to compete, he can insure the buyer against the risks involved in his continued competition. The court's view that such contracts, if reasonably restricted as to area, should be deemed valid is, therefore, unexceptionable. Such contracts are usually advantageous to both buyer and seller, and they do not ordinarily seriously injure the public by restricting competition. One competitor in the trade—the seller—drops out, but his place is taken by the buyer, often a newcomer in the trade.⁵

The objection that the older cases made to contracts which prohibited the buyer from engaging in the same line of business anywhere in England was equally sound. Until recently business was a local affair and, as the court said in *Mitchel v Reynolds*⁶ "What does it signify to a tradesman in London what another does at Newcastle?" Unfortunately, some modern courts have adhered to the old rule despite changed conditions and have held that agreements not to compete, which cover an entire state, are invalid even though they are made in connection with the sale of a business which has a statewide or even a nationwide clientele.⁷ A few state legislatures have unwisely enacted statutes which so provide.⁸ Happily, such statutes are comparatively rare, and most of those modern courts which are unhampered by statute have held that the proper test is whether the restraint is no wider than the area of the business, not whether it is narrower than the boundaries of the state.⁹

The question whether a contract which is unlimited in time is reasonable has also given the courts some trouble, but there is little or no dissent today from the proposition that the fact that a contract not to engage in business is unlimited as to time does not necessarily invalidate it, though the fact does have a bearing on the decision of the crucial question—whether the contract is unreasonable because more restrictive than is necessary to assure to the

⁵ The contract is, however, valid at common law even though the buyer was already engaged in the same line of business in the same locality so that the contract did in fact reduce the number of competitors.

⁶ 1 P Wms 181 (1711).

⁷ See *R L Polish v Schwartz*, 344 Ill 563 (1931). The contract did not relate to the sale of an entire business but to the sale of a large block of shares in a corporation by two of its officers. Three judges dissented.

⁸ See California Civ Code, §§ 1673-1675, 15 Oklahoma Stat Ann §§ 217-218. These statutes limit the permissible area to "a specified county, city or part thereof."

⁹ See 5 Williston on Contracts (Rev Ed 1937) § 1639 and cases cited. The problem does not seem to have arisen with respect to sales of a medical or dental practice.

buyer the goodwill of the business which he has purchased¹⁰ Contracts which, if literally construed, would be unlimited as to time are often construed as limited to a reasonable time and upheld as so construed

It is by no means obvious that contracts for the sale of a medical practice ought to be treated by the courts in the same manner as contracts for the sale of a business No doubt the interests of the seller and the buyer of a practice are substantially the same as those of the seller and the buyer of a grocery store In each case the seller wants to get the highest possible price for what he sells, which he cannot do unless he can make an agreement that will protect the buyer against the seller's competition In each case the buyer wants that protection—even more strongly perhaps in the case of the purchase of a medical practice A doctor who is selling his practice is likely to have much closer personal relationships with his patients than a grocer has with his customers, so that his continuing competition is likely to be more dangerous to the buyer than would be the case in the grocery business

On the other hand the interest of the public in having the seller free to continue his activities is much greater in the case of doctors than of grocers So much of medicine is a matter of understanding the individual patient's physical, mental and moral characteristics rather than of professional skill in the abstract that there is a very real loss to the patients of an experienced physician when he retires from practice, even where he sells his practice to one of equal ability If the selling physician later wants to resume practice, there is a very real hardship on his patients if he must refrain from doing so because of a contract that he has previously made

An agreement by a member of a healing profession that he will no longer heal the sick in the same community is one for which those who like to think of the medical profession as concerned primarily with community service and only incidentally with the pursuit of gain are likely to feel considerable distaste Nevertheless, it would probably have been unwise for the courts, in the absence of any indication that the community or the medical profession regards a doctor's agreement not to compete with the purchaser of his practice as anti-social, to refuse to accord legal validity to such an agreement

At all events, the courts have determined the validity of an agreement by a doctor or a dentist not to compete with the purchaser of his practice by the same standards which they apply to determine the validity of a similar agreement by a grocer By applying such standards they have in almost every case held such contracts valid¹¹ Few, if any, such contracts have been

¹⁰ See 5 Williston on Contracts (Rev. Ed. 1937) § 1638 and cases cited

¹¹ The cases upholding such contracts are numerous and the following list is not exhaustive In most of them the contract was held to be not only valid in law but enforceable in equity by injunction

(a) Contracts by a physician or other medical practitioner not to compete with one who is purchasing his practice

Doty v Martin, 32 Mich. 462 (1875) (unlimited contract not to practice in vicinity of Maple Rapids), *Wilkinson v Colley*, 164 Pa. 34, 30 Atl. 286 (1894) (contract not to practice within 8 miles of Lehman Centre for 10 years), *Gordon v Fairfield*, 84 Mo. App. 366

found to exceed the proper space limitations, and most courts hold that no time limitation is necessary¹² In one unusual case the contract not to compete was made by the buyer instead of by the seller The former, a proctologist, had purchased a sanatorium in Omaha from the latter and had gone into possession, but had paid only a small part of the purchase price He agreed that if he failed to pay the balance, he would not practice medicine within 150 miles of Omaha The agreement was held valid¹³

b The purchaser's remedies If the seller's agreement not to compete is legally valid and is broken by him, the buyer is, of course, entitled to the ordinary remedy for breach of contract—an action at law for damages Such a remedy is, however, an unsatisfactory one It is impossible to determine the amount of the damages which the buyer of a business or of a professional practice suffers by reason of the seller's competition Moreover, the bringing of an action for damages is not likely to put an end to the competition Since damages in an action at law are limited to those suffered up to the date of the beginning of the action, the buyer would, in case the seller's competition continued, be obliged to bring a series of actions for damages in order to get any effective relief

A much more effective remedy than that of damages is an injunction against the continuation of the wrongful competition This remedy can, in those states which adhere to traditional procedural methods, be obtained only by bringing a suit in equity rather than an action at law Equitable remedies are not given as a matter of right but as a matter of judicial discretion The plaintiff in a suit for equitable relief must convince the court that he needs the aid of equity because any legal remedy which he may have

(1900) (unlimited contract not to practice in county), *Wolff v Hirschfeld*, 23 Tex Civ App 670, 57 SW 572 (1900) (contract not to practice within 10 miles of Marion for 10 years), *Ryan v Hamilton*, 205 Ill 191, 68 NE 781 (1903) (unlimited contract not to practice within 8 miles of Viola), *Threlkeld v Steward*, 24 Okla 403, 103 Pac 630 (1909) (contract not to practice within 10 miles of Allen for 2 years), *Mills v Cleveland*, 87 Kan 549, 125 Pac 58 (1912) (contract by proctologist not to practice anywhere in the United States, broken by resuming practice in the same locality, a dubious decision in view of the scope of the contract), *Scott v Asbury*, 198 SW 1131 (Mo App 1917) (unlimited contract not to practice within 10 miles of Marceline), *Rowe v Toon*, 185 Ia 848, 169 NW 38 (1919) (contract not to practice in county for 10 years), *Clabaugh v Haebner*, 236 SW 396 (Mo App 1922) (unlimited contract not to practice in Green Ridge and vicinity), *Randolph v Graham*, 254 SW 402 (Tex Civ App 1923) (unlimited contract not to practice within a 20-mile radius), *Johnson v McIntyre*, 309 Pa 191, 163 Atl 290 (1932) (contract not to practice within a 15-mile radius for 15 years), *Johnson v Stumbo*, 271 Ky 301, 126 SW (2d) 165 (1938) (contract by a physician not to operate a hospital in the county in competition with a hospital which he was selling)

(b) Similar contracts by dentists

Dills v Doebler, 62 Conn 366, 26 Atl 398 (1892) (contract construed to permit resumption of practice on payment of a stipulated sum), *Socke v Murdock*, 20 N Mex 522, 151 Pac 298 (1915) (contract not to practice in Springer for five years), *Wall v Chapman*, 84 Okla 114, 202 Pac 303 (1921) (contract not to practice in city for five years), *Miller v Eller*, 192 Iowa 147, 183 NW 498 (1921) (contract not to practice in town for 25 years)

¹² But cf *Ral estraw v Lanier*, 104 Ga 188, 30 SE 735 (1898) (partnership agreement by physician not to practice within 15-mile radius after expiration of partnership held invalid because not limited as to time), *Manderville v Harmon*, 42 N J Eq 185 (VC 1886) (contract by physician not to practice in Newark at any time after the termination of his employment said to be of doubtful validity, injunction against breach refused)

¹³ *Tarry v Johnston*, 114 Neb 496, 208 NW 615 (1926)

s inadequate But since the only remedy at law which the buyer of a practice has against a seller who violates his agreement not to compete is an action for damages, and since that remedy is inadequate for the reasons above stated, the plaintiff's claim to the equitable remedy of an injunction is one which makes a very strong appeal to the courts If a promise made by the seller of a medical practice to the buyer that the former will cease to practice medicine is sufficiently limited in scope, if such promise is broken by the seller, and if the buyer seeks equitable relief by injunction instead of suing at law for damages, the injunction will be granted almost as a matter of course ¹⁴

c Implied agreements not to compete Doctors, like other people who make contracts, do not always express their meaning completely in the words of the agreement which they sign It not infrequently happens that a doctor agrees to sell his practice to another without any explicit statement as to whether the seller is to refrain from competition with the buyer Does such a sale imply an agreement not to compete?

The same problem has frequently been presented to the courts in the case of the sale of a commercial business A large majority of the courts have held that even where the contract for the sale of the business specifically states that the subject matter of the sale includes the good-will of the business, the buyer is free, nevertheless, to start a competing business next door and to serve his former customers, provided he does not personally solicit those customers to continue to deal with him and confines his efforts to attract their patronage to advertisements addressed not to them but to the community in general ¹⁵ This narrow view of what is meant by the sale of the good-will of a business has been justly criticized It is a fundamental principle of the law of sales that the seller of anything will be treated as impliedly agreeing not to derogate from his own grant Translated from legal jargon into plain English, this means that the courts will not permit a seller to do something inconsistent with what is fairly implied by his agreement of sale It is because of that principle that the courts have held that the seller of a business will not be permitted to solicit the business of his old customers by such methods as informing them that he is resuming business at a new address and hopes for their continuing patronage

Such a limitation on the buyer's rights is wholly inadequate The seller's goodwill, which he has expressly or impliedly sold, consists of the reputation that he has acquired with his customers ¹⁶ If he is allowed to resume busi-

¹⁴ Injunctions were granted in nearly all of the cases listed in footnote 10

¹⁵ 5 Williston on Contracts (Rev Ed 1937) § 1640

¹⁶ 5 Williston on Contracts (Rev Ed 1937) § 1640 A century or more ago Lord Eldon said that good-will "is nothing more than the probability that the old customers will resort to the old place" *Cantwell v Lyr*, 17 Ves 335 (1810) But the modern decisions recognize that the old customers tend to resort to the old trade-mark or trade-name and to the old individual as well as to the old place and that these tendencies are parts of the seller's good-will It is true that the purchaser of a business cannot take advantage of the tendency to resort to the old person, since he is a different person, but the seller can put an end to that tendency by going out of business If he does so that good-will which results to the buyer

ness operations in the neighborhood most of those customers will soon discover his new location, if they like his wares or his business methods (and unless some of them do he has no good-will to sell) many of them will continue to trade with him instead of transferring their patronage to the buyer of the business. It can, therefore, be argued convincingly that any selling to former customers is inconsistent with the seller's agreement to transfer his good-will to the purchaser. It would be impracticable, however, to permit the seller to do business and at the same time forbid him to serve such of his old customers as may come to him. The only effective way in which to give the buyer an adequate opportunity to obtain the good-will which he has bought is to treat the seller as having impliedly agreed not to compete at all.

The Massachusetts court has adopted substantially this view. It holds that a sale of a business implies a promise by the buyer not to compete in such a way as will deprive the buyer of the benefit of the good-will purchased.¹⁷ Although it is said to be a question of fact in each case whether competition will have such an effect, it is in practice usually found that it will have such an effect and that competition is therefore improper.¹⁸

The arguments for adopting this view are peculiarly strong in the case of the sale of a medical practice. Here it is abundantly clear that good-will does not mean primarily "the probability that the old customers will resort to the old place,"¹⁹ but the probability that they will continue to seek the services of the old man. Whatever may be true of a grocer, a doctor or dentist will lose few customers by moving, provided his new address is known and is reasonably convenient.

Some courts which do not accept the Massachusetts view with respect to the sale of a commercial business have held that the sale of a medical or other professional practice is distinguishable and that the latter does imply an agreement not to compete²⁰, in fact, there is very little direct authority against this view.²¹ The Massachusetts court has held that its rule that competition is always improper if it would deprive the buyer of the good-will necessarily makes all competition in the same locality by the seller of a medical practice unlawful, since in the case of a medical or dental practice

from the customers' tendency to resort to the old place of business or to the old name of the business will not be counteracted by the customers' tendency to continue to deal with the same man.

¹⁷ *Angier v Wakefield*, 11 Allen 211 (Mass 1867), *Old Corner Bookstore v Upham*, 194 Mass 101, 80 S E 228 (1907), *Martino v Pontone*, 270 Mass 158, 170 N E 67 (1930).

¹⁸ For cases in which continued competition by the seller was held not to be inconsistent with his sale of his good-will see *Horie v Chancy*, 143 Mass 592 (1887), *Fairfield v Lowry*, 207 Mass 352, N E (1911).

¹⁹ Lord Eldon, C in *Cantwell v Lye*, 17 Ves 335 (1810).

²⁰ *Brown v Benzinger*, 118 Md 29, 84 Atl 79 (1912) (chiropractist), *Yeakley v Gaston*, 450 Tex Civ App 405, 111 S W 768 (1908) (physician). See also *Townsend v Hurst*, 37 Miss 679 (1859) (physician).

²¹ In *Dillon v Nicodeme*, 117 S W (2d) 668 (Tex Civ App 1938), a chiropractor, who had bought the defendant's practice and good-will, was denied an injunction against the defendant, who had resumed practice in the same building. The court said that competition, without solicitation of former patients, did not violate the contract and that, furthermore, the plaintiff was not licensed to practice and could not legally do so. The court seems to have been unaware of its earlier remarks in *Yeakley v Gaston*, 50 Tex Civ App 405, 111 S W 768 (1908), *supra* note 20.

"the personal qualities of integrity, professional skill and ability attach to and follow the person not the place" ²² In Massachusetts the only difference in most cases between an express agreement by a seller not to compete and the agreement which is implied from his sale of the business is that in the first case the geographical limits which are expressly stated in the agreement will be approved by the court unless they are clearly broader than the area of the practice sold whereas in the latter case an implied limitation somewhat narrower than the area of the seller's practice may be deemed to give sufficient protection to the buyer. In *Foss v Roby*,²³ a retiring partner in a firm of Boston dentists sold his share of the good-will to his copartner and three years later resumed the practice of dentistry in that city. The court enjoined him from continuing to practice in Boston but limited the injunction to the city limits despite the fact that a considerable portion of the former partnership's business came from patrons living in other Massachusetts cities and towns. Presumably an express agreement not to compete would have been enforced as written even if the agreement had covered a considerably wider area than Boston.

Contracts by a Physician or Dentist Who Is Employed by Another Not to Compete with the Latter After the Termination of the Employment There is a wide variation among courts with respect to their general attitude towards contracts by an employee not to compete with his employer after the termination of the employment. The English courts declare that such contracts are quite different from contracts between the buyer and the seller of a business, and that in the former case an agreement not to compete is unreasonable and invalid in the absence of special circumstances making such a contract reasonably necessary for the protection of the employer.²⁴ A number of recent American decisions have taken a view substantially similar to that of the English courts²⁵, but many American courts make little distinction between contracts between buyer and seller and contracts between employer and employee.²⁶

There can be little question that the English view that the employer-employee situation differs radically from that of buyer and seller is sound.²⁷

²² *Foss v Roby*, 195 Mass 292, 297, 81 N E 199 (1907)

²³ 195 Mass 292, 81 N E 199 (1907)

²⁴ *Herbert Morris, Ltd v Savelby* [1916] A C 688

²⁵ *Clark Paper & Mfg Co v Stenacher*, 236 N Y 312, 140 N E 704 (1923), *Club Aluminum Co v Young*, 263 Mass 223, 160 N E 804 (1928) (but cf *Becker College of Business Administration & Secretarial Science v Gross*, 281 Mass 355, N E (1933), *Samuel Stores v Abrams*, 94 Conn 248, 108 Atl 54 (1919) (but cf *Torrington Creamery Co v Davenport*, 126 Conn 515, Atl (1940))

²⁶ See the numerous cases cited in 5 Williston on Contracts, § 1643 sustaining such contracts when made by employees

²⁷ But cf 5 Williston on Contracts (Rev Ed 1937) § 1643 "The ultimate question should be the same in both cases,—what is necessary for the protection of the promisee's rights and is not injurious to the public." To state the "ultimate question" that way is to treat the inequality of bargaining power between employer and employee and the hardship which such contracts impose on employees as legally irrelevant considerations. It is true that our nineteenth century common law of contracts tended in general to ignore such factors and that twentieth century limitations on the legal power of employers to exact unfair agreements from their employees have come about mainly through legislation. But in this particular subject—contracts in restraint of trade—the older common law tradition recognized the

Contracts to refrain from competition are contracts in restraint of trade. They are, therefore, invalid unless they are reasonable. The question of reasonableness involves a consideration of the interests of each of the parties to the contract and also of the public interest. There is first of all the promisee's interest. The purchaser of the good-will of a business always has an interest in preventing competition by the seller which tends to deprive him of the good-will which he has bought. The employer, on the other hand, is not buying good-will but services. Unless his employee has learned his trade secrets or become familiar with his customers, the employer has no greater interest in protection against the competition of his former employee than he has in protection against the competition of any other equally competent person—and the latter protection is something that the law refuses to give him even if he has bargained for it.²⁸

Moreover, the employee's interests also must be considered. A contract that he will not engage in competition with his former employer, either on his own account or as the employee of some one else, means that he must either change his line of work or his place of residence, even becoming an exile if his employer's business covers the whole country. He is likely to make such a contract at an early stage in his career, when most of his business or professional life lies before him. Such an agreement, if valid, will, as Lord Shaw of Dunfermline has said, be "subversive of the way of life to which [his] past special training has led up."²⁹ Moreover, there will in many, perhaps in most cases, be such inequality of bargaining power between employer and employee that the latter will get little or no compensation, other than temporary employment at current rates of pay, for agreeing to a restriction which affects his entire future business career. The situation is very different where the agreement is part of a bargain by which one who desires to retire from business agrees, for compensation, not to change his intention.

The injury to the public also is likely to be more serious in the employee case than in the sale case. In the former the public, or at least the local public, loses the services of one who is likely to be still young and vigorous, of one who has no desire to retire from active life. In the latter the public loses only the services of one who has already evinced an intention of retiring, though it is true that the legal validity of the agreement will not become important unless that intention changes.

The distinction between the English view and that taken by many American courts is, however, of little importance in the fields of medicine and dentistry. Doctors and dentists do not make restrictive agreements with

danger that "masters" would "give their apprentices much vexation" if the latter's agreements not to compete were held valid, and in general condemned such agreements. See *Mitchel v. Reynolds*, 1 P. Wms 181 (1711). The English courts have wisely adhered to the older view.

²⁸ Agreements not to compete made by one who is neither the seller of a business nor an employee or partner are ordinarily invalid as being in restraint of trade.

²⁹ See *Herbert Morris, Ltd v. Savelby* [1916] A.C. 688, 715.

their bookkeepers or office boys, but with their medical or dental assistants. Such assistants do come in contact with their patients. Frequently, they become better liked by some patients than the persons who employ them. Their competition after the termination of the employment would, therefore, be competition which would take advantage of relationships with patients established during the employment and by means of the employment. Such competition will apparently be enjoined even in England³⁰

Clearly, however, there are arguments on the other side. A man's customers do not belong to him as his trade secrets do.³¹ To oblige him to compete with his former employee may be annoying to him, but it involves little real hardship. To deny the former employee the right to continue to practice his profession without moving to a new community is exceedingly harsh. To deprive those patients who prefer the former employee's professional services to those of any one else of services which he is eager to give them is a hardship on them as well as on him. Contracts of the sort we are discussing, made by physicians or dentists—professions whose function like that of all true professions, is maximizing community service rather than maximizing profits—are not contracts in which public-spirited members of those professions can take pride. Yet such contracts, which must be fairly common since they have produced a considerable amount of litigation, are almost without exception upheld by American courts unless found to be of unduly broad scope.³²

³⁰ There are no recent English cases dealing with restrictive contracts between doctors, dentists or other professional men and their employers, but the language in the leading case of *Herbert Morris, Ltd v Saxeby* [1916] A C 688 indicates that such contracts, reasonably limited as to space, would ordinarily be held valid. The earlier cases so held *Davis v Mason*, 5 Term Rep 118 (1793) (contract by assistant surgeon not to practice within 10 miles of his former employer's residence for 14 years held valid), *Mallon v May*, 11 M & W 653 (1843) (contract by dentist's assistant not to practice in London or certain other towns held valid as to London), *Dendy v Henderson*, 11 Exch 194 (1855) (contract by solicitor's clerk not to act as such in the vicinity for 21 years held valid), *Lewis & Lewis v Dunford*, 24 T L R 64 (Ch D 1907) (contract by a solicitor's clerk not to "act for any person who is or has within the previous 5 years been a client of the firm" held valid).

³¹ No doubt an employer's list of customers is his property but the question is whether the employee can serve his former employer's customers, not whether he can legally copy his employer's list of customers.

³² The cases upholding such contracts are numerous and the following list is not exhaustive. In most of them the contract was held not only valid at law but enforceable in equity by injunction.

(a) Contracts by a physician or other medical practitioner with an assistant by which the latter agrees not to practice for a certain time after the termination of the employment.

Styles v Lyon, 87 Conn 23, 86 Atl 564 (1913) (unlimited contract by doctor's assistant not to practice in same town, injunction held properly limited to time during which former employer should continue to practice), *Freudenthal v Espey*, 45 Colo 488, 102 Pac. 280 (1909) (contract by doctor's assistant not to practice in same city for 5 years), *Granger v Craven*, 159 Minn 296, 199 NW 10 (1924) (contract by doctor's assistant not to practice within 20 miles of Rochester for 3 years), *Foster v White*, 248 N Y App Div 451, 290 N Y Supp (2d) 394 (1936) (unlimited contract by doctor's assistant not to practice in county). But see the same case on a subsequent appeal, *Foster v White*, 253 N Y App Div 448, 3 N Y Supp (2d) 456 (1938). It appeared that the plaintiff had improperly terminated the defendant's employment and he was accordingly denied an injunction against the defendant's practicing), *Wilson v Gamble*, 177 Miss, 363, 177 So 363 (1937) (contract by two doctor's assistants not to practice within 5 mile radius for 5 years), *McMurray v Faust*, 224 Ia 50, 276 NW 95 (1937) (contract by doctor's assistant not to practice in

Moreover, such contracts, like other contracts not to compete, are usually treated as entitling the promisee to an injunction and not merely to damages. That view has not been universally adopted, however. A few courts have recognized the harshness of such contracts to the extent of saying that a court of equity will not grant an injunction against the breach of such an agreement by the doctor's or dentist's assistant unless the court is convinced that competition by the latter would impose severe hardship on his former employer.³³

Contracts by Partners Not to Compete Both in business and in the medical and dental professions agreements not to compete are frequently made between partners. In some cases the agreement is made at the time when some partner retires from the firm, in which case the agreement is, in effect, an agreement for the sale of his part of the firm's good-will to his co-partners.³⁴ In other cases such agreements are made when a partnership is formed or when a junior partner, often one who has previously been an employee, is admitted to the firm, in which case the partner's contract not to compete closely resembles an employee's contract not to compete after the termination of his employment. Similar agreements are sometimes made by physicians who are associated in some way, but are not partners or at any rate do not regard themselves as such. Agreements of these various types, when made by physicians or dentists, are almost without exception held valid and enforced by means of an injunction.³⁵

county for 5 years), *Laisen v Bunnoughs*, 224 Ia 740, 277 NW 403 (1938) (contract by doctor's assistant not to practice in same town for 10 years)

(b) Similar contracts by dentists

Tillinghast v Boothby, 20 RI 59, 37 Atl 344 (1897) (contract by dentist's assistant not to practice in county), *Turner v Abbott*, 116 Tenn 718, 94 SW 64 (1906) (unlimited contract by dentist's assistant not to practice in vicinity), *Erickson v Hawley*, 12 F (2d) 491 (DC Ct App 1926) (contract by orthodontist's assistant not to practice in District of Columbia for 10 years)

In *Olsen v Swendiman*, 62 ND 649, 244 NW 870 (1932) a contract by a dentist's assistant not to practice in the same or a neighboring city for two years was held invalid because in violation of a North Dakota statute.

In *Lair v Stearman*, 264 Ill 110, 105 NE 957 (1914) a contract by a dentist with his employer, who was not a dentist, that the former would not practice within a 25-mile radius was construed to deny him the right to practice even if he carried out the terms of an agreement which entitled him to buy the business. It was held unreasonable and invalid.

³³ In *Osius v Hinchman*, 150 Mich 603, 114 NW 402 (1908) the court recognized the validity of a contract by a dentist's assistant not to practice in Muskegon for five years, but refused to enforce it by an injunction. Cf *Schneller v Hayes*, 176 Wash, 115, 28 Pac (2d) 273 (1934) in which an optician's employee had agreed never to do business as an optician in the city. His employment was an employment at will and the court said that the agreement was too one-sided to be enforced in equity.

³⁴ The following cases involve contracts of this type. *Latham v Butler*, 17 SW (2d) 1083 (Tex Civ App 1929) Two physicians had been co-owners of a hospital and had operated it as partners. Defendant sold out to plaintiff who agreed to pay all the partnership debts and to employ defendant for one year, defendant agreeing not to practice in the county thereafter. The agreement was enforced by injunction. *Sover v Buck*, 351 Ill 643, 184 NE 840 (1933) A retiring member of a medical partnership agreed for consideration not to practice in the same city. The agreement was held valid.

The following cases involve contracts of these types. *Glover v Shirley*, 169 Mo App 637, 155 SW 878 (1913) (agreement made by a junior partner on being admitted to a firm that he would not after leaving it practice within a 10-mile radius for 10 years, enforced by injunction), *Marcel v Jonah*, 83 N J Eq 295, Atl (Ct Err & App 1914) (agreement

SUMMARY

Judicial hostility to agreements in restraint of trade would undoubtedly make a promise by a doctor or dentist not to practice his profession invalid, where such promise was unconnected with the sale of a practice, or with an employment, a partnership or some similar type of association. Where, however, as is usually the case, the person to whom such promise is made is a purchaser of a practice or an employer or partner of the promisee, the agreement is almost universally found to be reasonable and lawful. Whether it is desirable to treat such agreements not to practice one's skill in the art of healing as valid and binding is a question of social policy, on which neither a judge nor a law teacher is ex officio an expert.

by a junior partner that, if the partnership were ever dissolved by reason of his violation of the partnership agreement, he would not practice in the city for three years, enforced by injunction), *Proctor v Hansel*, 205 Ia 542, 218 NW 255 (1928) (promise by young osteopath, as part of an agreement by which he was associated with an older man, that after the termination of the arrangement he would not practice osteopathy in the city for three years, enforced by injunction), *Shaleen v Strattle*, 188 Minn 219, 246 NW 744 (1933) (provision of partnership agreement that on the termination of the partnership one partner would not practice medicine in either of two counties for five years, enforced by injunction), *Heirington v Hackler*, 181 Okla 396, 74 Pac (2d) 388 (1937) (provision in partnership agreement between two doctors who owned a hospital that if the partnership proved unsatisfactory, defendant would either buy out the plaintiff or turn the hospital over to him and refrain from practicing for five years within a radius of 100 miles, stipulation against practicing enforced by injunction).

But cf *Rakestraw v Lanier*, 104 Ga 188, 30 SE 175 (1898) in which a provision in a partnership agreement that at its expiration one of the partners would not practice medicine within a 15-mile radius was held invalid because unlimited as to time.

TORT LIABILITY OF HOSPITALS *

By AUSTIN WAKEMAN SCOTT, † *Cambridge, Massachusetts*

MANY are the situations in which the activities of a hospital may cause damage to someone, who thereupon brings an action for tort against the hospital. An action for tort is a civil proceeding brought by the complaining person to recover damages from the person or corporation charged with causing the injury. The injury may be to the person of the plaintiff or to his property. We are not concerned with the liability of the individual who caused the injury but only with that of the hospital itself. We are not concerned with liability for breach of contracts made by the hospital. We are not concerned with questions of criminal liability. We are concerned only with the question of the liability of hospitals to pay damages for injury to person or property.

The cases in which actions have been brought against hospitals, which are scattered through the volumes of the state and federal reports, would fill several volumes. These reports as a rule contain only cases which have been carried to the higher courts, and there are, of course, numerous cases which have not been appealed to the higher courts. They show the kinds of claims which may be made against hospitals. They involve claims that a physician or surgeon was negligent in the treatment of a patient, that an operation was performed without the consent of the patient, that a nurse left sponges in a patient's body, or burned an unconscious patient with a hot water bottle, or gave a patient the wrong medicine, that an ambulance driver negligently ran over a pedestrian, that a roentgen-ray technician negligently burned a patient, that incompetent nurses were employed, that the floors were slippery or the stairs unlighted; that a newborn baby was given a bed instead of a bassinet, that insane patients were permitted to leap from windows, that insane patients were maltreated by attendants, that patients having contagious diseases were not properly segregated, that a fire resulted from defective wiring, that patients were neglected, that an elevator was defective, that unwholesome food was served, that driveways were unlighted or sidewalks defective, that the property of patients was negligently lost, that the hospital was so conducted as to disturb persons living nearby. In all of these cases someone was negligent or guilty of willful misconduct and someone else was injured. In all of these cases the question arose whether the hospital corporation was subject to liability.

An individual is liable to a person who suffers damage as a result of his negligence. So also, he is liable for damage caused by the negligence of an employee acting within the scope of his employment. This general principle of tort liability is applicable to corporations. A corporation is liable for

* Received for publication January 28, 1943.
† Dine Professor of Law, Harvard University.

damage caused by the negligence of its officers or directors or employees acting within the scope of their employment. The question which we have to consider is whether and to what extent a hospital is exempt from such liability.

To the extent to which a hospital is entitled to exemption from tort liability it is on the ground that it is a charitable corporation. The question of the exemption of hospitals is a phase of the broader question of the exemption of charitable institutions. A similar question arises as to the exemption of educational institutions, religious organizations, homes for orphans or for the aged, and institutions of other sorts for the benefit of the community, such as Young Men's Christian Associations. The purposes for which these institutions are created and maintained are charitable purposes. Undoubtedly, also, the promotion of health is a charitable purpose, whether the purpose is the prevention or cure or treatment of diseases or other human ills of the flesh.

A distinction must be made, however, between proprietary and charitable institutions. Just as a school which is conducted for private profit is not a charitable institution, although it promotes education, so also a hospital or nursing home conducted for profit is not a charitable institution, although it promotes health. Just as such proprietary institutions are not exempt from taxation, so they are not exempt from tort liability. It is a proprietary institution where the profits, if any, are to be devoted to private uses, as where they go into the pockets of those who own the institution. The mere fact, however, that in the conduct of the institution profits are earned does not make the institution a proprietary one, if the profits must be used in furthering the charitable work of the institution. The fact that the recipients of benefits are compelled to pay for the services they receive if they are financially able to pay does not prevent the institution from being a charitable institution, and this is true, although there is some conflict in the decisions of the courts, even though no services are rendered gratuitously. Thus, a hospital which is not privately owned is none the less charitable although most, if not all, of its patients are paying patients.

What is the basis for the claim of exemption from tort liability of charitable institutions, including hospitals? Three possible bases have been suggested by various courts in their decisions.

(1) The first suggested basis is that where property is devoted to charitable objects it should not be diverted from those objects, and that to compel the corporation to use its property in paying claims of persons who have been injured is such a diversion. This is sometimes called the "trust-fund theory." Thus, in a case in Massachusetts,¹ the court stated as a reason for exempting a hospital from tort liability that "being a charitable institution rendering services to the public without pecuniary profit, if the property of the charity was depleted by the payment of damages its usefulness might be

¹ *Farrigan v Pricar*, 193 Mass 147, 149, 78 N E 855 (1906)

either impaired or wholly destroyed, the object of the founder or donors defeated, and charitable gifts discouraged "

Under this theory the exemption of the hospital is very broad Under it the hospital is not subject to liability whether the negligence is that of the directors or trustees or officers or that of its nurses or other employees, it is not subject to liability whether the person injured is a patient, either a paying patient or a charity patient, or is a visitor or employee or a stranger, as for example a person who is injured on the sidewalk in front of the hospital or a person who is struck by an ambulance

(2) Another suggested basis is that of waiver or implied agreement The theory is that a person who receives the services of a hospital impliedly agrees to waive the right to hold the hospital liable for any injuries he may receive at the hospital In the Massachusetts decision just cited the court stated as a ground for exemption that "if an individual accepts the benefit of a public charity he thereby enters into a relation which exempts his benefactor from liability for the negligence of servants who are employed in its administration, provided due care has been used in their selection "

Such a waiver, it seems clear, is purely fictitious It certainly is inapplicable to injured persons other than patients It does not apply to strangers, such as pedestrians, who are injured by the negligent driving of an ambulance, it does not apply to injured employees of the hospital, it does not apply to visitors who are injured on the hospital premises, as, for example, those who fall on an improperly lighted stairway or on a slippery floor It applies to charity patients It is generally held to apply also to paying patients, although there seems to be little basis for the notion that a patient who pays for the service rendered by the hospital agrees to waive any claim against the hospital The courts, however, have generally felt that it would be an invidious distinction if they were to hold that damages could be recovered by a paying patient, but none could be recovered by a charity patient Moreover, even the paying patient seldom pays the full cost of the service rendered

(3) A third suggested basis of exemption is that the doctrine under which an employer is liable for the negligence of his employee, the so-called doctrine of *respondeat superior*, is not applicable to charitable institutions The suggestion is that this doctrine should be limited to undertakings carried on for the profit of the employer, business and not charitable undertakings Under this theory there can be no recovery against the hospital by anyone, whether patient or visitor or employee or stranger, where the injury results from the negligence of a mere employee of the hospital, whether janitor, ambulance driver, orderly, nurse or physician or surgeon Thus, in a case in Connecticut,² where an action was brought against a hospital for injury caused by the negligence of an employee of the hospital, the court said "The law which makes one responsible for an act not his own, because the actual

² *Hearn v. Waterbury Hospital*, 66 Conn 98, 123, 125, 33 Atl 595, 603, 604 (1895)

wrongdoer is his servant, is based on a rule of public policy. The liability of a charitable corporation for the defaults of its servants must depend upon the reasons of that rule of policy, and their application to such a corporation.

This defendant does not come within the main reason for the rule of public policy which supports the doctrine of *respondeat superior*, it derives no benefit from what its servant does, in the sense of that personal and private gain which was the real reason for the rule."

On the other hand, under this theory the hospital is not exempt from liability for the negligence of the governing board or of the administrative officers of the hospital. Thus, the hospital is liable where the injuries result from the negligent selection or retention of incompetent employees, from the failure to make proper rules for the conduct of the institution, or from negligence in permitting the premises to be in a dangerous condition. A distinction is drawn under this theory between the negligence of those higher up and the negligence of a mere employee.

None of the suggested reasons for exemption is altogether satisfactory and in most of the states no one theory is consistently applied. The rules in the various states as to the exemption of hospitals from tort liability vary greatly. At one extreme are states like Massachusetts which go the full length in giving exemption, no matter who is injured and no matter who among the officers or employees of the hospital by his negligence caused the injury. At the other extreme are jurisdictions like the District of Columbia where the Court of Appeals has held that an institution is entitled to no exemption from liability in tort merely because it is a charitable institution. In other states the courts have taken some intermediate view, some of them holding that a hospital is exempt from liability to its patients, but is not exempt from liability to other persons, such as employees, visitors or strangers, others holding that a hospital is not liable for the negligence of mere employees but is liable for the negligence of its governing board or officers. A review of the more recent decisions shows a trend toward the limiting or the abolition of the exemption of hospitals and other charitable institutions.

The rule in the District of Columbia was laid down for the first time in a recent case in which a hospital was held liable to the plaintiff, a special nurse, who was injured when a student nurse violently pushed a swinging door which struck the plaintiff. Judge Rutledge, after a careful examination of the decisions in the various states with their "welter of conflict," and after examining and rejecting the various bases on which exemption has been granted, held that the fact that the defendant is a charity gives it no immunity. He said, "The rule of immunity is out of step with the general trend of legislative and judicial policy in distributing losses incurred by individuals through the operation of an enterprise among all who benefit by it rather than in leaving them wholly to be borne by those who sustain them. The rule of immunity itself has given way gradually but steadily through widening, though not too well or consistently reasoned, modifications. It is

disintegrating Each modification has the justification that it is a step in result, if not in reason, from the original error toward eventual correction As more and more steps are taken, correction becomes more complete The process is nearing the end" He said that insurance should be carried to guard against liabilities and concluded "To offset the expense [of insurance] will be the gains of eliminating another area of what has been called 'protected negligence' and the anomaly that the institutional doer of good asks exemption from responsibility for its wrong, though all others must pay The incorporated charity should respond as do private individuals, business corporations and others, when it does good in the wrong way"³

No matter what view may be taken as to the liability of a hospital for the negligence of persons employed by it, the hospital is under no liability to persons injured through the negligence of one who was not in the employment of the hospital In such a case the hospital is under no liability, not because of an exemption given to charitable institutions but because the general doctrine of *respondeat superior*, the doctrine that an employer is responsible for his employee's acts, is not applicable to the particular situation There are numerous cases holding that the hospital is not liable because the negligence was that of a physician or surgeon or nurse who was employed by the patient and not by the hospital In a leading New York case,⁴ a woman sued a hospital alleging that the house physician discovered a lump which proved to be a fibroid tumor, and that he consulted the visiting physician who advised an operation, and that she consented to an examination but not to an operation, and that while she was under ether the operation was performed and that gangrene developed This testimony was disputed, but the court held that even if it were true the hospital was not liable Judge Cardozo said.

³ *President and Directors of Georgetown College v Hughes*, 130 F (2d) 810, 827, 828 (App DC 1942)

In this case Judge Rutledge drew the following conclusions as to the state of the law in the various states, recognizing, however, that it is difficult in some of the states to determine the precise rule there prevailing

Full immunity, except perhaps for administrative negligence or in special cases Arkansas, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Missouri, Oregon, Pennsylvania, South Carolina, Wisconsin

Full liability District of Columbia, Minnesota, New Hampshire, New York, and probably Oklahoma Also England, Canada and New Zealand

Recovery by strangers and paying patients but possibly not charity patients Alabama, California, Florida, Georgia, Idaho, Oklahoma, Utah

Recovery by strangers but not patients Connecticut, Indiana, Iowa, Louisiana, Michigan, Nebraska, New Jersey, North Carolina, Ohio, Rhode Island, Texas, Virginia, Washington

No recovery by patients but no decisions as to strangers Arizona, Maine, Mississippi, Montana, Nevada, West Virginia, Wyoming

Liability if protected by insurance Colorado, Tennessee

No decisions Delaware, New Mexico, North Dakota, South Dakota, Vermont

For collection of cases on the liability of hospitals, see 49 A L R 379 (1927)

As to the liability of charitable corporations in general, see 14 A L R 572 (1921), 23 A L R 923 (1923), 30 A L R 455 (1924), 33 A L R 1369 (1924), 42 A L R 971 (1926), 62 A L R 724 (1928), 86 A L R 491 (1933), 109 A L R 1199 (1937), 124 A L R 814 (1940), 133 A L R 821 (1941) See Scott, *Trusts* (1939, Supp 1942) § 402

⁴ *Schloffer v New York Hospital*, 211 NY 125, 131, 132, 105 NE 92, 94 (1914)

"The wrong was not that of the hospital, it was that of physicians, who were not the defendant's servants, but were pursuing an independent calling, profession sanctioned by a solemn oath, and safeguarded by stringent penalties. If, in serving their patient, they violated her commands, the responsibility is not the defendant's, it is theirs. There is no distinction in that respect between the visiting and the resident physicians. Whether the hospital undertakes to procure a physician from afar, or to have one on the spot, its liability remains the same.

"It is true, I think, of nurses as of physicians, that in treating a patient they are not acting as the servants of the hospital. The superintendent is a servant of the hospital, the assistant superintendents, the orderlies, and the other members of the administrative staff are servants of the hospital. But nurses are employed to carry out the orders of the physicians, to whose authority they are subject. The hospital undertakes to procure for the patient the services of a nurse. It does not undertake through the agency of nurses to render those services itself."

It is to be noted that the hospital is not liable for the negligence of a nurse where the nurse is not an employee of the hospital but is employed by the patient, and even if the nurse is an employee of the hospital, it is not liable for her negligence when she is acting under the direct authority of a physician or surgeon.

In a recent New York case,⁵ where a patient gave his dentures to a special nurse engaged for him by the hospital, it was held that the nurse was not an employee of the hospital, and if the teeth were lost as a result of the negligence of the nurse, the hospital was not liable.

On the other hand, even if a person, as for example a roentgen-ray technician, is not an employee of the hospital, the hospital may be liable for injury if it has represented that he is its employee.⁶

The question has occasionally arisen whether a hospital or other charitable institution is subject to liability where it has taken out insurance against liability, although it would otherwise be exempt. It has been held in a number of cases that it is immaterial that the hospital is insured.⁷ This is on the ground that the insurance is only against legal liability and there is no legal liability, with the result that the insurance company receives the premiums but runs no risk. The result is, it would seem, unfair to the hospital which pays the premiums and unfair to the person who is injured. It would seem more equitable to interpret the insurance policy as an agreement to save the hospital harmless not only from claims that would otherwise be legally enforceable but from any claims which could be enforced against it if it were not a charitable institution. There is recent authority to the effect that where the

⁵ *Fisher v Sydenham Hospital, Inc.*, 176 Misc. 7, 26 N.Y.S. (2d) 389 (1941).

⁶ *Stanhope v Los Angeles College of Chiropractic*, 128 P. (2d) 705 (Cal. App. 1942).

⁷ See *Levy v Superior Court*, 74 Cal. App. 171, 239 Pac. 1100 (1925), *Williams' Adm'x v Church Home*, 223 Ky. 355, 3 S.W. (2d) 753 (1928), *Enman v Trustees of Boston University*, 270 Mass. 299, 170 N.E. 43 (1930), *Mississippi Baptist Hospital v Moore*, 156 Miss. 676, 126 So. 465 (1930), *Herndon v Massey*, 217 N.C. 610, 8 S.E. (2d) 914 (1940).

hospital has liability insurance, the injured person can recover damages from the hospital not exceeding the amount of the insurance, even though in the absence of such insurance the hospital would be exempt.⁸

Whatever rule is applied to privately endowed hospitals, it is generally held that a hospital maintained by a state or a political subdivision of the state, such as a county or municipality, is exempt from liability, as is the state or county or municipality.⁹

In states in which hospitals are exempt from liability in tort, the exemption is applicable not only in the case of personal injuries but also in the case of property damage. Thus, in a case in Ohio,¹⁰ it was held that a patient could not recover for the loss of jewels entrusted to the hospital for safekeeping and lost through the negligence of the custodian in handing them over to an imposter.

In states in which hospitals are exempt from liability in tort, a patient who has suffered injuries as a result of the negligence of an employee of the hospital cannot recover damages against the hospital on the theory that it has made a contract for careful treatment.¹¹

Even in states in which a hospital has immunity from liability for tort committed in its administration, it can be enjoined from maintaining a nuisance. Thus, in a case in Pennsylvania¹² the complainants were the owners of a house adjoining a hospital which maintained an operating room the windows of which faced the house at a distance of from 9 to 12 feet, with the result that the moans, shrieks and groans of persons receiving surgical aid "were of such a character as to render wretched the lives of complainants, and of friends visiting them, and were such as to affect their nerves and impair their health." It further appeared that persons occupying rooms in the hospital were permitted to throw refuse across the fence and upon complainants' property. The court awarded an injunction, ordering the removal of the operating room to some other part of the building and restrained the defendant from permitting persons occupying rooms in the hospital to throw refuse matter upon complainants' property. There are other cases also in which hospitals were so conducted as to constitute a nuisance and in which the court ordered the abatement of the nuisance.¹³

⁸ *O'Connor v Boulder Colorado Sanitarium Ass'n*, 105 Colo 259, 96 P (2d) 835 (1939), *Vanderbilt University v Henderson*, 23 Tenn App 135, 127 S W (2d) 284 (1938). See *Lusk v United States Fidelity & Guaranty Co.*, 199 So 666 (La 1941).

⁹ *President and Trustees of the University of Louisville v Metcalfe*, 216 Ky 339, 287 S W 945 (1926). See a note in 49 A L R 379 (1927) on liability of hospital maintained at expense of state or a political subdivision for torts of its officers or employees.

¹⁰ *Rudy v Lakeside Hospital*, 115 Ohio St 539, 155 NE 126 (1926).

¹¹ *Waltman v St Luke's Hospital Ass'n*, 314 Ill App 244, 41 NE (2d) 314 (1942), *Roosen v Peter Bent Brigham Hospital*, 235 Mass 66, 126 NE 392 (1920).

¹² *Kestner v Homeopathic Medical and Surgical Hospital*, 245 Pa 326, 91 Atl 659 (1914).

¹³ *Draconess Home and Hospital v Bontjes*, 207 Ill 553, 69 NE 748 (1904), *Heir v Central Kentucky Lunatic Asylum*, 97 Ky 458, 30 S W 971 (1895), 110 Ky 282, 61 S W 283 (1901).

COMPULSORY VACCINATION AND STERILIZATION: CONSTITUTIONAL ASPECTS¹

By THOMAS REED POWELL, *Cambridge, Massachusetts*

ANY statute or administrative order authorizing or compelling involuntary medical or surgical treatment has the possibility of being scrutinized and countermanded by the Supreme Court of the United States. Where the deed is done before the Supreme Court can forbid it, there still may be suits against the perpetrators for damages, and the Supreme Court can decide whether the statute relied on for justification is one entitled to constitutional sanction. In deciding such issues the Supreme Court has no other primary guide than the provision of the Fourteenth Amendment to the Federal Constitution that "No State shall deprive any person of life, liberty, or property, without due process of law, nor deny to any person within its jurisdiction the equal protection of the laws." As a guide to judgment, this is no guide at all. Nevertheless the Supreme Court has for years, in the name of these provisions, condemned legislation that a majority of its members deemed to be sufficiently arbitrary and unreasonable. The exercise of this power has not been confined to the procedures by which governmental action is taken, but has extended to the substance of the commands and prohibitions.

Few, if any, are likely to contend that this power has invariably been wisely exercised. On several issues the average of the Supreme Court is zero. The Court has held that an employer may not be forbidden to exact as a condition of employment that the employee will not become or remain a member of a labor union. The Court has held the contrary. It has similarly reversed itself on the issue of a 10 hour limitation of labor in factories and on the issue of legislative prescription of a minimum wage for women in industry. In thus referring to "the Court" as though it were a continuing body, a caution would be necessary if it were not so obvious. Although through the somersault of Mr. Justice Roberts, the same bench both condemned and sustained a minimum wage law, usually any decided shift in decision comes after a shift in the composition of the tribunal. This could not be denied as a matter of fact. Yet what to a plain man would seem a necessary inference from the fact, is not so universally acknowledged.

The law books have been full of foolish statements from judges which would make them out to be mere automatons in applying meaningless constitutional phrases to determine the validity of statutes. From dissenting judges, however, often comes the charge that the majority have unjustifiably transformed their own views of public policy into constitutional commands or prohibitions. Most amusingly a distinguished lawyer and former judge

* Received for publication February 13, 1943

in protesting against the President's so-called "court packing plan" asserted the theory of judicial automatism, apparently unaware that if it made no difference who was on the bench, it made no difference who was on the bench. We know well enough from recent history that it does make a difference. We have seen too many new judicial attitudes substituted for former ones. Not a few of them have been direct and confessed recantations. Others have been decisions which clearly would not have been reached by an earlier bench but which found no direct precedents in their way. Still others have been decisions accompanied by opinions which made such sleazy distinctions between the case at bar and its predecessors that it was apparent to persons with a modicum of discernment that the current had changed its course.

From this propensity of judges to pretend that they are consistent with the past when it is obvious that they are not, arises a major difficulty in prophesying what they will do next. The old precedents hang on, not overruled. A later court may follow them and rely on the unjustifiable distinction drawn in the interim. Or the unjustifiable distinction may be repeated a number of times and later be officially recognized as a contradiction rather than a distinction and hence an inflicter of a mortal wound on the law that lived before. Such are the perils to prophecy when it is pretty obvious that the judicial distinctions are skating on very thin ice. When it is not obvious, the lot of the would-be prophet is certainly no happier. There are too many cases where clearly tenable distinctions have been made the sensible basis of judgment and yet have later turned out to be forerunners of an erosion or an abandonment of what had been well established earlier. An expert can report what a court has said and done and can weave it all into an apparently neat and harmonious pattern. It still remains true that it is often a gamble to try to forecast what the court will say and do next.

Akin to the difficulties of prophecy when there are a number of decisions and opinions to be taken into consideration is the difficulty of knowing how wide is the scope of a single decision. By approved canons a court wisely confines itself to the decision required by the facts, and technically the decision, as distinguished from dictum, does not extend beyond the issue or issues which must be settled to dispose of the dispute. Yet often the reasons given in the court's supporting opinion warrant the belief that the principle on which the decision rests is broad enough to embrace a much wider range of facts. Nevertheless later the decision may be narrowly limited to the minimum grounds sufficient to support it. On the other hand, a court in deciding a case may lay stress on each individual element so as to leave itself unfettered by precedent when presented with a new problem containing any variant in the facts. Seldom are two cases exactly on all fours. When they are, there is not likely to be litigation unless a contender fights chiefly for delay or is ready to bet that a court will change its mind. Almost always there is the question whether the differences in the facts are enough to make a difference in result. Hence the law remains a congeries of particulars but imperfectly subsumed under general principles.

One aspect of this perennial problem of uncertainty appears in *Jacobson v Massachusetts*¹ which in 1905 by a vote of seven to two sustained a compulsory vaccination law. The particular statute vested power in Boards of Health to require vaccination when in their opinion it was necessary to the public health. There was an exception in favor of children who present a certificate, signed by a registered physician, that they are unfit subjects for vaccination. There was no such exception in favor of adults. The adult convicted of violating the statute by refusing to comply with an order did not allege that he was in fact an unfit subject for vaccination. He did not present or ask leave to present any physician's certificate. Smallpox was prevalent to some extent in the city at the time of the Board's order. The defendant sought to introduce evidence tending to show the ineffectiveness and the dangers of inoculation. The evidence was excluded by the trial court. On this state of facts, the conviction was sustained by the Supreme Court of the United States. The compulsory requirement was held under the circumstances to be within the police power of the state for the protection of health.

We must go to the opinion of the Court to attempt to ascertain how far the decision goes. The refusal to hear the evidence offered by the defendant was justified on the ground that it went only to a dispute between two theories. The Court knew judicially (i.e., without having to take formal evidence) that the theory favoring vaccination accords with common belief. It said that it must assume that the state was not unaware of the opposing theories and that it was compelled of necessity to choose between them. This, it had power to do. "It was not compelled to commit a matter involving the public health and safety to the final decision of a court or jury."² This declaration, isolated from the rest of the opinion, would seem to go far to sanction all sorts of compulsory inoculation for all sorts of menaces however disputable and disputed their value. But the Court had pointed out that vaccination was favored by "common belief."³ It cited legislation in England beginning in 1808 which encouraged or compelled vaccination. The Court knew what every other sensible person knew, and this knowledge lay in the background of its decision and opinion and must be recognized in qualification of occasional statements of broad general tenor.

Thus, as the decision does not go beyond vaccination against smallpox, so it does not surely go beyond compulsion when the malady is prevalent. For after invoking recitals of such prevalence in the order of the Board of Health, the opinion continued

"If such was the situation,—and nothing is asserted or appears in the record to the contrary,—if we are to attach any value whatever to the knowledge which, it is safe to affirm, is common to all civilized peoples touching smallpox and the methods most usually employed to eradicate that disease, it cannot be adjudged that the present

¹ 197 U S 11 (1905)

² *Id* at 30

³ *Ibid*

regulation of the board of health was not necessary in order to protect the public health and secure the public safety. Smallpox being prevalent and increasing at Cambridge, the court would usurp the functions of another branch of government if it adjudged, as matter of law, that the mode adopted under the sanction of the state to protect the people at large was arbitrary, and not justified by the necessities of the case. We say necessities of the case, because it might be that an acknowledged power of a local community to protect itself against an epidemic threatening the safety of all might be exercised in particular circumstances and in reference to particular persons in such an arbitrary, unreasonable manner, or might go so far beyond what was reasonably required for the safety of the public, as to authorize or compel the courts to interfere for the protection of such persons" ⁴

Here is warning enough that the Court is going only so far as the particular circumstances require. A more specific caveat appears in the treatment of the apparent absoluteness of the statute in dealing with adults. Although it was held to be a reasonable classification for the statute not to embrace adults in an exception in favor of children presenting a physician's certificate of unfitness for vaccination, this holding was substantially nullified by saying that there might be extreme cases in which the Court would interfere and by in effect importing into the statute a dispensation for abnormal adults. After saying that general language should be interpreted to exclude injustice, oppression, or an absurd consequence, the opinion continues:

"Until otherwise informed by the highest court of Massachusetts, we are not inclined to hold that the statute establishes the absolute rule that an adult must be vaccinated if it be apparent or can be shown with reasonable certainty that he is not at the time a fit subject of vaccination, or that vaccination, by reason of his then condition, would seriously impair his health, or probably cause his death. No such case is here presented" ⁵

This does not say that an adult who failed to make any appearance to claim a dispensation could escape from punishment by later evidence before a court. It does not say with certainty that failure to excuse an adult with a certificate would render compulsory vaccination unconstitutional. It seeks to avoid the issue by suggesting to the state court that it should read an exception into the statute. Such a hint would in all likelihood be taken by state courts. Such exceptions should be accorded by any sensible Board of Health without advice from any legislature or court, if there were reasonable grounds for confidence in the certifying physician. Doubtless in some fashion the dispensations have been granted if requests have been made, for the Supreme Court has had no subsequent controversy presenting the issue for formal adjudication. Its caution in favor of individualization must have been heeded widely. Constitutional law is permeated with similar cautions against extreme and unusual applications of statutes found not objectionable in general. The cautions have not infrequently been translated into condemnations. Particularity is of the essence of constitutional law, as it is a major theme of this effort at diagnosis.

⁴ 197 U. S., at 27-28

Id. at 39

Although the Court saved itself from sanctioning compulsory vaccination except when smallpox is in the vicinage, it must be doubted whether this condition would be insisted upon. Some state courts in construing broad powers vested in School Boards and Boards of Health to take action to protect the public health have drawn the distinction between seasons of epidemic and the absence thereof. The cases are not recent ones, and they are not to be commended for good sense. A stitch in time saves nine, and the time to lock the barn is before the horse is stolen. At any rate where legislative authority to compel vaccination is explicitly conferred, it is unthinkable that at this late date a court would say that the vague due process clause forbids precaution and requires procrastination until the presence of pestilence. Common sense forbids us to believe that judicial sanction of compulsion in time of epidemic carries with it a negative pregnant that compulsion is unconstitutional otherwise.

One other observation in the opinion deserves mention. After referring to the liberty of a person to live and work where he will, it is added that "yet he may be compelled, by force if need be, against his will and without regard to his personal wishes or his pecuniary interests, or even his religious or political convictions, to take his place in the ranks of the army of his country, and risk the chance of being shot down in its defense"⁶. This was not pertinent to the case at bar except for pointing out that personal liberty is not absolute. Mr Jacobson advanced no objections on conscientious or religious grounds. Yet one wonders whether the Court did not mention religion in order to forestall any claims of conscience against health laws. Some queer sects do raise such objections. Other more numerous religionists object to some other compulsions affecting bodily integrity. Such objections have sometimes prevailed with legislatures. They may have influenced some state courts even though they have not been the explicit basis of decision. Thus far, however, it cannot be said that they have carried weight with the United States Supreme Court. This brings us to another topic.

In 1927 in *Buck v Bell*⁷ the Supreme Court by a vote of eight to one sustained a sterilization statute. In 1942 in *Skinner v Oklahoma*⁸ it unanimously condemned another one. Our problem is to try to guess whether the later decision indicates a total or partial recantation of the earlier one or whether it indicates merely that a state must provide adequate safeguards and move within a restricted area when it commands the extinction of procreative power. On the facts there is the clearest distinction between the two cases. The Virginia statute sustained in *Buck v Bell* applied only to mental defectives confined in institutions and it provided elaborate procedure for notice, hearing and appeals. Miss Buck was a feeble-minded daughter of a feeble-minded mother and a feeble-minded mother of a feeble-minded daughter. Mr Justice Holmes declared that "The principle that sustains

⁶ *Id.* at 29

⁷ 274 U. S. 200 (1927)

⁸ 316 U. S. 535 (1942)

compulsory vaccination is broad enough to cover cutting the Fallopian tubes"⁹ and that "Three generations of imbeciles are enough"¹⁰ Mr Justice Butler dissented, but since he gave no opinion we do not know whether he would think that we needed six or a dozen such generations instead of a meager three

In *Buck v Bell* there was no attack on the procedure required by the statute and scrupulously followed in the particular case. There was criticism that equal protection was denied because the statute applied only to those confined in institutions and not to the multitudes outside. This was easily met by the general rule of reasonable classification and by the more special retort that "Of course so far as the operations enable those who otherwise must be kept confined to be returned to the world, and thus open the asylum to others, the equality aimed at will be more nearly reached"¹¹ On the substantive issue, the brief on behalf of Miss Buck did not adduce any religious grounds. It asserted that the operation is unrelated to health or morals, and that the right to bodily integrity is an absolute one. In rejecting the contention Mr Justice Holmes went further than was his usual custom and indicated affirmative approval of the state's policy when he said

"We have seen more than once that the public welfare may call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the state for these lesser sacrifices, often not felt to be such by those concerned, in order to prevent our being swamped with incompetence. It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind"¹²

Turning now to the condemnation visited on the other statute in *Skinner v Oklahoma* the main concern should be that of the psychologist or the psychiatrist rather than any expert in black letter law. The interesting thing about the decision is that seven members of the Court refrained from passing any judgment on the underlying issue of permanent significance. They condemned the statute solely for discrimination and in the particular case because it applied to triple offenders who commit larceny but not to those who commit embezzlement. This, they held to be a denial of equal protection of the laws. The defect could readily be remedied by an amendment embracing embezzlers. Then one or two more fundamental issues would have to be faced. One of them was faced by Mr Chief Justice Stone when he concurred on the sole ground that the statute afforded to the prospective victim no opportunity to show that his criminal tendencies are not of an inheritable type. With this, Mr. Justice Jackson agreed. He also agreed that the discrimination against thieves as contrasted with embezzlers offends against

⁹ 274 U S, at 207

¹⁰ *Ibid*

¹¹ 274 U S, at 208

¹² *Id* at 207

the requirement of equal protection of the laws. He disagreed with each of the other two opinions "in so far as it rejects or minimizes the grounds taken by the other" ¹³

There must have been some reason why eight members of the Court thought it important to lay stress on the discrimination point and why seven wished to do nothing more. In general the fact that a statute doesn't go so far as it reasonably might has not in recent years been a basis for condemnation. Mr Justice Douglas in the opinion of the Court gives general recognition of this in quoting with approval from *Buck v Bell* the statement that "the law does all that is needed when it does all that it can, indicates a policy, applies it to all within the lines, and seeks to bring within the lines all similarly situated so far and so fast as its means allow" ¹⁴. He, however, then goes on to point out that this particular legislation "involves one of the basic civil rights of man" ¹⁵ and elaborates on the possibility of its application as a weapon of discrimination against a particular race or nationality ¹⁶.

The cases cited for these views are ones involving members of the Chinese and colored races. Such invocation suggests that the judges were less concerned with the triviality of the distinctions between larceny and embezzlement than with the desirability of setting up a barrier against legislative race discrimination. While they emphasize the severe and irrevocable deprivation from sterilization, they say that they do so not to re-examine the scope of the police power of the state. Clearly what they most fear is that sterilization may be employed as a weapon of class hostility. It would seem that they would not trust the safeguard of a hearing on the individual's potentiality of communicating criminal traits, for they refrain from joining with the Chief Justice on this point. Even with the safeguard of a hearing, there could be discrimination in administration merely by refraining from proceeding against those of a preferred class. The case does not reveal to what race the petitioner belonged. The first of his three convictions was for stealing chickens. The case came from Oklahoma. Oklahoma has been

¹³ 316 U S, at 546

¹⁴ *Id* at 540, quoted from 274 U S, at 208

¹⁵ 316 U S, at 541

¹⁶ "Marriage and procreation are fundamental to the very existence and survival of the race. The power to sterilize, if exercised, may have subtle far-reaching and devastating effects. In evil or reckless hands it can cause races or types which are inimical to the dominant group to wither and disappear. There is no redemption for the individual whom the law touches. Any experiment which the State conducts is to his irreparable injury. He is forever deprived of a basic liberty. We mention these matters not to re-examine the scope of the police power of the States. We advert to them merely in emphasis of our view that strict scrutiny of the classification which a State makes in a sterilization law is essential lest unwittingly, or otherwise, invidious discriminations are made against groups or types of individuals in violation of the constitutional guaranty of just and equal laws. The guaranty of 'equal protection of the laws' is a pledge of the protection of equal laws." *Pick Wo v Hopkins*, 118 U S 356, 369. When the law lays an unequal hand on those who have committed intrinsically the same quality of offense and sterilizes one and not the other it has made as invidious a discrimination as if it had selected a particular race or nationality for oppressive treatment. *Pick Wo v Hopkins*, *supra*, *Gawis v Canada*, 305 U S 337" (316 U S, at 541)

rebuked by the Supreme Court in other matters in which racial issues were involved¹⁷

In certain sections of the country the possibility of a considerable degree of racial discrimination would be present in a statute dealing with all habitual criminals as determined by three convictions for felony. One can hardly say that there was no warrant for this judicial emphasis on discrimination, though one must wonder somewhat why there was unwillingness to join in the objection to lack of a hearing on the issue of transmissibility in the individual case. Even if the Chief Justice's sole reliance on the absence of a hearing might on its face suggest a possible negative pregnant that there was no other substantive defect, Mr. Justice Douglas protected himself and his seven colleagues from any complicity in such an inference by saying explicitly of all objections other than that of discrimination that "we pass those points without intimating an opinion on them"¹⁸. Nor does he anywhere seem to intimate any opinion except as to the fundamental nature of the civil right involved and the danger of its invasion as a weapon of discrimination. It is unthinkable that he and those for whom he wrote would not insist upon a hearing even in a non-discriminatory law. Hence in the absence of any knowledge of what went on in conference, one can only venture the notion that they thought or felt that it would emphasize the menace of class discrimination if it were made the exclusive basis of condemnation.

The Chief Justice, though technically he confines himself to the absence of a hearing, intimates a doubt whether criminality is physically transmissible. In objecting to basing the decision on discrimination he says

"Moreover, if we must presume that the legislature knows—what science has been unable to ascertain—that the criminal tendencies of any class of habitual offenders are transmissible regardless of the varying mental characteristics of its individuals, I should suppose that we must likewise presume that the legislature, in its wisdom, knows that the criminal tendencies of some classes of offenders are more likely to be transmitted than those of others"¹⁹

And later, in a passage which seems to reaffirm *Buck v Bell* and to point a difference between the statute there and the one before the court, he adds

"Science has found and the law has recognized that there are certain types of mental deficiency associated with delinquency which are inheritable. But the State does not contend—nor can there be any pretense—that either common knowledge or experience, or scientific investigation, has given assurance that the criminal tendencies of any class of habitual offenders are universally or even generally inheritable"²⁰

These two passages make it extremely likely that the Chief Justice would scrutinize severely any finding by physicians that any individual would be likely to breed criminals merely because he had been thrice convicted him-

¹⁷ See *Gunn v United States*, 238 U S 347 (1915), *Lane v Wilson*, 307 U S 268 (1939)

¹⁸ 316 U S, at 538

¹⁹ *Id* at 544

²⁰ *Id* at 545

self It would seem that at most he would be satisfied only by other findings of physical and mental degeneracy comparable to those made in the case of Miss Buck

Mr Justice Jackson in his special concurrence clearly intimates that he thinks a fundamental constitutional issue would remain even if the defects of discrimination and absence of hearing were cured He does not even go so far as to give clear approval to *Buck v Bell* when he merely recites the fact that "This Court has sustained"²¹ the compulsion under the particular circumstances there existing This is quite different from the Chief Justice's statement that "Undoubtedly a state may"²² compel what was sanctioned in *Buck v Bell* Quite frequently during the current judicial dispensation, mere recitals of former rulings and of the grounds which predecessors adduced for them have been indications of a disposition to qualify or reject rather than to reaffirm While to Mr Justice Holmes his reference to three generations of imbeciles may have been merely a superfluous rhetorical rivet, its repetition by Mr Justice Jackson may possibly be designed to turn it into a more or less essential condition Should any such requirement be judicially imposed, the state would find it more practical to deal with habitual offenders by stone walls and iron bars rather than by the surgeon's knife

So much for what Justices of the United States Supreme Court have said and done The recital does not throw much light on what they or their successors would do with milder eugenic measures, except to make clear that they would be zealous in insisting upon strong scientific support for the necessity and the efficacy of prophylactic prescriptions and upon adequate procedural safeguards in picking the persons subjected to them A materialist might find it somewhat sentimental to emphasize the sacredness of procreative power when for habitual offenders there may be deprivation of all opportunity for its exercise There are, however, other than materialistic elements in the problem, ones that in certain tightly knit fellowships would obtain even if the state did no more than to proffer sterility as the price of release from long prospective incarceration From a practical standpoint such release would mean the relinquishment of the most adequate safeguard against continued criminal enterprise by an already practiced and proficient offender

If all this seems sadly vague and amorphous to those who extract certainties out of test tubes, it can only be answered that of such is the kingdom of jurisprudence Even in the kingdom of the healing art one does not always find complete concord and certainty One who listens to the nauseating promulgation of nostrums on the radio must turn in increased confidence to the more modest and tentative approach of the physician The sin of the law is not that it is empirical and particularistic but that so often it professes to derive from the universal and the absolute This is especially foolish when courts exercise power over legislatures in the name of un-

²¹ *Id* at 546

²² *Id* at 544

enlightening constitutional cautions Happily the practice not only does not accord with the profession, but is far superior Strange as it may seem that we have a system of government under which five lawyers on a bench in Washington can say "No" when a state legislature and a state court have said "Yes" and base their negative on their views of social policy, it would be hard to maintain that there was not wisdom in making a distinction between the case of Mr Skinner and that of Miss Buck

There is nothing in the law books which would give a lawyer any special competence to pass judgment on what the Supreme Court would say about other eugenic measures less drastic than sterilization and more far reaching and invasive than vaccination The immediacy of danger from contagious and infectious diseases, the substantial certainty of a fair degree of efficacy from recognized curative and preventive measures, the avoidance of finality in their application—these and other considerations should keep the decision in *Skinner v Oklahoma* from being a stumbling block in the way of any sane public health program however much it may intrude on privacy and preclude self-determination There are, of course, sects which don't believe in medicine at all and other sects which object to the intrusion of animal substances, but the time has not yet come when their tenets are likely to carry even subconscious weight with the Supreme Court as claimants for inclusion in the protection surrounding civil or religious liberty Whether they may in some areas have weight with state legislatures and state courts is somewhat less certain Voters may carry weight by their numbers quite as much as by their reason

One final point may deserve mention If the Supreme Court is satisfied that a measure belongs in the field of public health and is not patently or covertly punitive in design, the intervention of a jury is not necessary in the determination of the facts in the individual case This is established by *Buck v Bell* and by *Minnesota ex rel Pearson v Probate Court*,²³ subject always to the qualification that precedents continue to be followed The *Pearson* case involved the commitment of a so-called "psychopathic personality" to an institution Except for the intervention of a jury, the proceedings before the Probate Court and on appeal were scrupulously protective against the danger of error As to the compulsory appointment of two physicians to assist in the examination, the Court said that "The argument that these doctors may not be sufficiently expert in this type of cases merely invites conjecture There is no reason to doubt that qualified medical men are usually available" ²⁴ Such faith should be welcome to the medical profession. It would be an extreme legalist who could say as much for the general run of jurors Some, of course, may question the infallibility of judges, but under our system they have the final say if duly invited to say it

²³ 309 U S 270 (1940)

²⁴ *Id* at 276

THE DOCTOR'S FEDERAL TAXES *

By ERWIN N. GRISWOLD, † *Cambridge, Massachusetts*

DURING the period of the first world war, the maximum amount which was raised by taxes in any one year was \$5,400,000,000. Our present tax laws are yielding more than five times that amount, and the President's budget message for 1943 asks for additional taxes which will greatly increase the present total. Tax rates have necessarily gone steadily higher while exemptions have gone lower, and there are very few in the community now who do not feel directly the burden of federal tax collection.

The modern income tax dates from 1913, in which year the Sixteenth Amendment to the Constitution was adopted.¹ Since that time Congress has adopted many revenue laws, and at the present time the income tax is a very refined and exceedingly complex instrument. We often hear pleas that the tax laws should be simple so that every citizen might easily know his duties and responsibilities. But experience has shown that this cannot be. A simple income tax could be drawn, but it would be full of harsh unfairnesses on the one hand, and loopholes on the other. As tax rates go higher, it has been necessary to introduce many new provisions into the law to alleviate burdens and prevent escape. Fortunately, however, many of the more complex sections have no application to the ordinary taxpayer.

The body of the tax law is contained in the Internal Revenue Code. This is a codification of the tax statutes which was adopted by Congress in 1939, and references in this article to sections are to the sections of the Code, including the numerous amendments which have been adopted in the past four years. In addition to the statute, there is a great mass of other materials which may have bearing on the solution of a tax problem. Pursuant to authority granted in the statute, the Commissioner of Internal Revenue issues a large quantity of regulations. These represent the official interpretation of the law, and in many situations have much the same force and effect as if Congress had itself adopted them. In addition, there are many administrative opinions and rulings by the Revenue authorities. These are published weekly in the Internal Revenue Bulletin, and twice a year are gathered into a volume known as the Cumulative Bulletin. Finally, there are many thousands of decisions of the courts which have interpreted and applied the various provisions of the statute. These start with the Tax Court of the United States, known until recently as the Board of Tax Appeals, which turns out over a thousand tax decisions a year. But tax cases

* Received for publication January 28, 1943.

† Professor of Law, Harvard Law School.

¹ The Sixteenth Amendment provides: "The Congress shall have power to lay and collect taxes on incomes, from whatever source derived, without apportionment among the several States, and without regard to any census or enumeration."

This was made necessary by the unfortunate decision of the Supreme Court in 1895 in *Pollock v. Farmer's Loan & Trust Co.*, 158 U. S. 601.

are also being constantly decided by the federal District Courts, the Circuit Courts of Appeals, and by the Supreme Court. These are the materials which must be consulted on any difficult point in the tax law. There is much that is very difficult, but there is also, fortunately, a large area in which the application of the tax is fairly certain.

THE INCOME SUBJECT TO TAX

The tax is imposed on *net income*, which consists of gross income less certain deductions and credits (or exemptions). Thus we must start with *gross income*, and we find that it is defined in very sweeping terms. Section 22 (a) of the Code provides that " 'Gross income' includes gains, profits, and income derived from salaries, wages, or compensation for personal service of whatever kind and in whatever form paid, or from professions, vocations, trades and businesses, commerce, or sales, or dealings in property, also from interest, rent, dividends, securities, or the transaction of any business carried on for gain or profit, or gains and profits and income derived from any source whatever."

Specifically, this means that the doctor must include in gross income all of his fees, any salary he may have, either from a medical school or clinic, or from any one else by whom he may be employed, and also any dividends, interest, rent or other income which he may have. The Supreme Court has held that this section "indicates the purpose of Congress to use the full measure of its taxing power within those definable categories."² There are only a few items of receipts which are expressly exempted from the tax. These include gifts and inheritances,³ the proceeds of life insurance payable by reason of the death of the insured,⁴ and amounts received as compensation for personal injuries or sickness.⁵ But except for these specific items, the sweep of the definition of gross income is very great, and reaches to every item of receipts of every individual.⁶ And the receipts need not be in cash. The value of any property or benefit received is subject to the tax.

² *Helvering v. Clifford*, 309 U. S. 331, 334 (1940).

³ Section 22(b)(3). A receipt is not a gift unless it is purely gratuitous. It does not have to be paid pursuant to a strict contract or after sending a bill, to be income. Thus, if a doctor renders professional services, and the patient thereafter sends in a check without any agreement or bill, the entire amount is income, even though it is more than the bill which the doctor would have sent for the services.

⁴ Section 22(b)(1). The exemption applies even where the proceeds of the insurance are payable in installments, as in the form of an annuity payable to the decedent's widow for her life. In such a case a portion of each payment to the widow is (from the insurance company's point of view) income on the money left with the company. But several cases have held that the entire amount of such payments is exempt from income tax. *Commissioner v. Winslow*, 113 F. (2d) 418 (C.C.A. 1st, 1940), *Commissioner v. Bartlett*, 113 F. (2d) 766 (C.C.A. 2d, 1940), *Allis v. LaBudde*, 128 F. (2d) 838 (C.C.A. 7th, 1942), *Kaufman v. United States*, 131 F. (2d) 854 (C.C.A. 4th, 1942). The Treasury has now accepted this view, T. D. 5231, issued February 22, 1943.

⁵ Section 22(b)(5).

⁶ The proceeds from the sale of property are not income to the extent that they represent a return of capital or investment. Thus if property costing \$800 is sold for \$1,000, \$1,000 is received, but only \$200 is income. The amount to be included in "gross income" may be reduced by the provisions of the statute dealing with capital gains. Section 117.

Thus the value of board and room is taxable, if it is received as compensation for services,⁷ and the same rule applies to an automobile or other thing of value which might be received from a grateful patient

Accounting Methods Since the income tax is imposed on a periodic basis, it becomes necessary to determine in many cases the period for which an item should be reported as gross income. Two principal methods of accounting are recognized for tax purposes, and either one may be adopted by an individual taxpayer. The method most widely used by individuals is the *cash* method. This means that income is reported for the period within which it was *received*, and deductions are taken for the period when they were *paid*. This is the simple method, and is usually quite satisfactory for most persons whose income is chiefly from a salary or fees. Some questions can arise. For example, income is received when a check is received, at least if the check was thereafter paid in due course. Thus a check mailed on December 31 and received on January 2 is taxable as income for the later period.⁸ On the other hand, some items are taxable on the cash basis, even though they have not been received. This is called constructive receipt, and applies to items which are unqualifiedly subject to the taxpayer's demand. Examples of such items are savings bank interest which is taxable though not withdrawn, matured bond coupons, and a drawing account, where the taxpayer is taxable on the amount he can withdraw whether he does withdraw it or not.

The other method of accounting is the *accrual* basis. Most business organizations make their returns on this basis, and an individual can do so if he chooses.⁹ On this basis, an item is taxable as income for the period when it *accrues*, and an item may be deducted for the period within which it is *incurred*. The time of receipt or payment is immaterial. This method more accurately reflects the economic return for the efforts of a given period, since the time of actual collection or payment may in many cases be largely fortuitous. Under the accrual method a doctor would report his fees as income for the period within which they were billed, and the time of actual collection would not affect the tax. Of course some of the fees billed will not be collected, and a deduction is allowed for bad debts at the time they become worthless,¹⁰ or a reserve may be set up for bad debts, and reasonable additions to this reserve may be deducted in each period. Where the cash method is used, uncollectible fees do not give rise to any deduction for a bad

⁷ Sec 1922(a)-3 of Regulations of 103 provides "If services are paid for with something other than money, the fair market value of the thing taken in payment is the amount to be included as income."

⁸ *Avery v Commissioner*, 292 U S 210 (1934)

⁹ Although either method may be chosen, a taxpayer who has adopted one method may not change to the other unless he obtains the permission of the Commissioner of Internal Revenue. Thus, persons who have heretofore used the cash method must continue on that basis unless they seek and obtain the required permission.

¹⁰ Sec 23(k) of the Code. Until recently the bad debt deduction was very technical, and required that the debt be both "ascertained to be worthless" and "charged off" during the taxable year. This was changed by the Revenue Act of 1942 to allow the deduction simply of "Debts which become worthless within the taxable year."

debt, since they have never been included in income. They are simply income which the taxpayer hoped to get but never did, and are thus neither income nor a basis for deduction.

DEDUCTIONS

After the gross income has been ascertained, there is naturally much interest in determining the deductions. The statute allows the deduction of interest payments,¹¹ taxes,¹² business losses, and losses of property arising from "fires, storms, shipwreck, or other casualty, or from theft,"¹³ bad debts,¹⁴ and charitable contributions.¹⁵ Probably the most important deduction in many cases is that allowed for "All the ordinary and necessary expenses paid or incurred during the taxable year in carrying on any trade or business."¹⁶ Under this provision, a doctor may deduct his office rent, fuel, water, light, telephone, and supplies for office use, and any professional expenses,¹⁷ such as dues in medical societies, subscriptions to medical journals,¹⁸ and travelling and other expenses in attending medical conventions.¹⁹ In an

¹¹ Sec 23(b)

¹² Sec 23(c) But federal income taxes are not deductible (state income taxes paid may be deducted in computing the federal tax), nor may any deduction be taken for inheritance, estate or gift taxes. Assessments made for special benefits, such as improving a street, are not deductible, they are treated as an addition to the cost of the property benefited. Taxes may be deducted only by the person on whom they are imposed as taxes. It is not enough that the economic burden is borne by the person claiming the deduction. Thus a tax imposed on a manufacturer cannot be deducted by the purchaser even though the amount of the tax is included in the purchase price. For this reason, the federal tax on gasoline is not deductible by the consumer. Nor may the federal taxes on liquor or tobacco or on retail sales (such as the tax on silver and jewelry) be deducted by the purchaser. Sec 23(c)(3) was added to the Code by the 1942 Act to provide that state retail sales taxes may be deducted by the purchaser regardless of whether he actually pays it as tax or as an addition to the purchase price.

The taxes which may be deducted include those on admissions, club dues, safe deposit boxes, telephone bills and telegraph messages, state income taxes, state or local taxes on land and personal property (other than benefit assessments as indicated above), taxes on railroad tickets, poll tax, automobile taxes, stamp taxes on transfers of stocks, bonds and real estate, and any tax which a doctor may have to pay in order to dispense narcotics.

¹³ Sec 23(e).

¹⁴ Sec. 23(k)

¹⁵ Sec 23(o) The amount deductible for charitable gifts is limited to 15 per cent of the net income (computed without taking charitable contributions into account)

¹⁶ Sec 23(a)(1)(A)

¹⁷ Sec 19.23(a)-5 of Regulations 103 "Professional expenses—A professional man may claim as deductions the cost of supplies used by him in the practice of his profession, expenses paid in the operation and repair of an automobile used in making professional calls, dues to professional societies and subscriptions to professional journals, the rent paid for office rooms, the cost of the fuel, light, water, telephone, etc., used in such offices, and the hire of office assistants. Amounts currently expended for books, furniture, and professional instruments and equipment, the useful life of which is short, may be deducted."

¹⁸ It has been held in several cases that amounts expended by a physician for railroad fare, hotel accommodations and meals in connection with attending meetings and conventions of medical societies is deductible as an ordinary and necessary expense. *Cecil M. Jake*, 13 BTA 726 (1928), *J. Bertley Squirr*, 13 BTA 1223 (1928), *Roy Upham*, 16 BTA 950 (1929), *Robert C. Coffey*, 21 BTA 1242 (1931), *Wolfe v. McCaughn*, 17 AFTR 1007 (C.D. Pa. 1933). The Bureau of Internal Revenue now follows this view. IT 2602, X-2 Cum Bull 130 (1931).

¹⁹ Of course, the expenses deductible are those of the physician himself. They do not include the expenses of his wife and family who may accompany him. Nor do they include purely recreational expenses, such as the cost of a side trip made on the way to or from the convention.

early ruling it was held that the expenses of doctors in taking postgraduate courses in schools were deemed to be personal expenses, and thus not deductible²⁰ It is far from clear, though, that this ruling would be followed now

Another item of expenditure which is clearly deductible on the doctor's income tax return is the amount of wages and salaries paid to any employees These may be salaries paid to office employees, such as receptionists or nurses, or to technicians or to other doctors who may be in the taxpayer's employ The only restriction that the statute puts on the deduction of such items is that they be "a reasonable allowance for personal services actually rendered"²¹ Thus a salary paid which under the circumstances was so large as to amount to a gift would not be deductible beyond the amount of reasonable compensation Such a payment would be subject to particular scrutiny where the payee was the taxpayer's wife or other relative A payment by way of pension is deductible, however, where it is reasonably related to past services rendered²²

A new provision added to the Revenue Act of 1942 makes it possible now to deduct expenses incurred in connection with the production of taxable income, even though they are not connected with the taxpayer's trade, business or profession²³ Under this clause, deductions may be had for costs incurred in connection with the management and protection of investments, such as the cost of a safe deposit box²⁴ or the expenses of a custodian or advisor in supervising and handling the investments This section also makes it clear that the expenses of investment in real estate, including depreciation, may be deducted on the tax return

Personal Expenses The statute expressly provides that "Personal, living, or family expenses," may not be deducted²⁵ This prevents the deduction of the cost of the taxpayer's home, his clothes, his food, the expenses of his children, including the cost of their schools, camps, or other care Similarly, wages paid to household or domestic employees are not deductible The Treasury has recently ruled that examination fees and other expenses paid by physicians for securing the right to practice their profession are personal expenses and may not be deducted This applies also to the basic cost of obtaining a medical education²⁶ Similarly, the cost of insurance on the taxpayer's house or personal automobile (not used for business) is a personal expense, and is not deductible For the same reason, life insurance

²⁰ O D 984, 5 Cum Bull 171 (1921)

²¹ Sec. 23(a) (1) of the Code

²² Compare the decision in *Waters F Burrows*, 38 BTA 236 (1938), where it was held that expenses of practicing medicine in previous years but paid in the current year by a doctor on the cash basis were deductible, even though he had retired from active practice before the expenses were actually paid

²³ Sec. 23(a) (2) of the Code, added by § 121 of the Revenue Act of 1942

²⁴ But only if the box is used for the protection of income producing property Thus no deduction is allowed for the cost of a safe deposit box used for jewelry, silverware or for fire insurance policies or the deeds to the taxpayer's own residence See § 1923(a)-15 of Regulations 103, added by T D 5196, Internal Revenue Bulletin, December 14, 1942 p 39, 42

²⁵ Sec. 24(a) (1) of the Code

²⁶ Sec. 1923(a)-15 of Regulations 103, added by T D 5196, Internal Revenue Bulletin December 14, 1942, pp 39, 41-42

premiums and premiums paid on health and accident insurance policies may not be deducted. But the cost of a doctor's insurance against liability for injuries to patients and claims for malpractice may be deducted, since that is an ordinary and necessary part of the expense of carrying on the profession.

In many cases the line between professional and personal expenses is far from clear. It has been particularly hard to draw this line in the case of uniforms worn by nurses, surgeons and others engaged in medical work. These are the personal attire of the persons wearing them, yet it is equally obvious that they are worn for professional purposes, and represent to a considerable extent an extra professional expense. There is an early ruling that these costs may not be deducted,²⁷ but there is reason to believe that the official view on this may have changed, at least where the article of clothing is "unsuited to wear outside of working hours."²⁸

Another instance of the line between personal and professional expenses is in the deduction for rent. If a doctor maintains an office separate from his home, the rent of the office is clearly deductible. But the rent of his home is not deductible, even though he receives occasional patients there. If, however, he maintains a separate portion of his home as an office in which patients are regularly received, then he may deduct the portion of his rent that is fairly attributable to the office.²⁹ The situation is similar as to the expenses of operating an automobile. If the car is used partly for personal use, and partly for professional calls, then a proper proportion of the expenses of gasoline, oil, repairs, and other costs of operation may be deducted. The cost of the car itself is not deductible for reasons which are stated in the next paragraph, but a similar proportion of the depreciation sustained on the car may be deducted. If the car is used entirely for professional purposes, then all the expenses of operation are deductible, including all of the allowance for depreciation.

Capital Expenditures Another line has to be drawn in the matter of deductions between what may be called current expenses on the one hand, and capital expenditures on the other. "Ordinary and necessary expenses" are deductible, but the cost of anything which amounts to a capital investment may not be deducted at the time of acquisition. The cost is instead recovered for tax purposes through a depreciation allowance spread over the life of the article. It is not always easy to decide whether an item may be deducted or must be capitalized, but a rough and ready test may be found by saying that if it will last more than about three years it must ordinarily be

²⁷ I T 1488, I-2 Cum Bull 145 (1922)

²⁸ See G C M 19662, 1938-1 Cum Bull 168, and G C M 19790, 1938-1 Cum Bull 118, where it was held that the cost of uniforms worn by jockeys and baseball players can be deducted. If doctors can bring themselves within this class they would seem to be entitled to the deduction, and there would seem to be no reason for a distinction—so far as this question is concerned.

²⁹ Sec. 1924-1 of Regulations 103. "In the case of a professional man who rents a property for residential purposes, but incidentally receives clients, patients, or callers there in connection with his professional work (his place of business being elsewhere), no part of the rent is deductible as a business expense. If, however, he uses part of the house for his office, such portion of the rent as is properly attributable to such office is deductible."

capitalized. A familiar example is an automobile used for business or professional purposes. The investment in an automobile is recoverable through depreciation allowances spread over the life of the car. For an ordinary passenger automobile this period is usually taken as about five years, and thus one-fifth of the cost is deductible in each of the first five years the car is owned. After the full cost has been made up by depreciation allowances, no further deduction can be had. Similar questions may arise with respect to books, and various items of professional equipment, ranging from typewriters to roentgen-ray machines and other items of a professional laboratory. Occasional books bought from time to time may ordinarily be deducted currently, but large sets or the cost of a professional library must ordinarily be recovered through depreciation.³⁰ Similarly, depreciation is allowable on a building owned by the taxpayer and used as an office, or held for investment, or against the proper proportion of the cost of the taxpayer's residence when he maintains an actual office in the building.

Where depreciation is taken against an item of property, the amount of depreciation allowed is deducted from the cost of the property to determine the taxpayer's remaining capital investment in it, for the purpose of computing gain or loss on a subsequent sale. Thus, if an automobile is purchased for \$1,000 and used solely for professional purposes for two years, during which depreciation was allowed at the rate of \$200 a year, the taxpayer's remaining capital investment would be \$600. If he then sold the car for \$700, he would have a taxable gain of \$100, although he sold the car for less than he paid for it. On the other hand, if he traded the car in on a new car for professional use, he would have no gain or loss on the trade,³¹ and the new car would take as its basis for depreciation the sum of the remaining basis on the old car plus the amount paid in cash to complete the trade. The same is true with respect to any other professional capital asset, such as typewriters, desks and other office furniture, and scientific instruments and equipment used for medical purposes.

CREDITS

In addition to the deductions, the statute provides for certain credits in the computation of net income which is subjected to the tax. The chief of these are the personal exemption and the credit for dependents. In the 1942 law the exemption is fixed at \$1,200 for a married couple or for the "head of a family," and \$500 for a single person. In addition to this a credit of \$350 is allowed for each dependent child under the age of eighteen, or for any

³⁰ The Treasury has published a pamphlet known as Bulletin 7 (1942 edition) which deals with depreciation allowances in some detail. The following appears at page 60 "Professional and Scientific Equipment. Under this heading will come libraries and equipment used in professional activities. The life usually applied to professional libraries is 30 years while the life for scientific equipment used by dentists, doctors, etc., is usually 10 years."

³¹ Sec. 112(b) (1) of the Code provides "No gain or loss shall be recognized if property held for productive use in trade or business is exchanged solely for property of a like kind to be held for productive use in trade or business."

dependent person, regardless of age who is incapable of self support because of mental or physical defects ³²

Earned Income The other credit allowed to individuals is the earned income credit ³³ This is available against the normal tax only, and is a credit of 10 per cent of the earned net income, and is deducted in the computation of net income subject to that tax. There are certain rather arbitrary limitations on the computation. The first \$3,000 of net income is treated as earned income regardless of its actual source, and in no case more than \$14,000 allowed as earned net income. With the normal tax rate at the present 6 per cent, the effect of the earned income credit is to reduce the tax payable by 6 per cent of 10 per cent of the amount of the earned net income. Thus the earned income credit never results in a saving of more than \$84 at the present rates, because of the top limit of \$14,000. The income received by a doctor from fees or salary is earned income even though a part of the work is done by employees and assistants under his general direction.

TAX REDUCTION

With tax rates already at unprecedented heights, it is natural that there should be much interest in devices which will help in tax reduction. During the past decade there has been a good deal of activity to this end, but much of it has saved no taxes and caused much expense and grief in the process. Some tax reduction is fairly obvious. Taxes can be saved by not going to the movies, and staying off trains, and not making long distance calls. It is also desirable for a taxpayer in these days to keep an adequate memorandum book in which he may make proper record of all items of deduction which he may claim on his return, such as all taxes paid, and items of business and professional expense, such as postage used at the office for sending out bills, and so on. A substantial percentage of all of these items can be saved when they are deducted from income at the present rates.

Beyond this the quest for tax reduction leads into the realm of trusts and transfers of property, and this is a field into which no layman should venture without the very best of experienced advice. This is not a plug for the lawyers, but merely a statement that a doctor should not try to deal with such a question on casual suggestions from a friend or a "tax expert" with a service to sell, any more than a lawyer should undertake self-medica-

³² Sec. 25(b) of the Code

³³ Sec. 25(a) of the Code

³⁴ Sec. 1925-2 of Regulations 103 "The entire amount received as professional fees may be treated as earned income if the taxpayer is engaged in a professional occupation, such as a doctor or a lawyer, even though he employs assistants to perform part or all of the services, provided the clients or patients are those of the taxpayer and look to the taxpayer as the person responsible for the services performed."

The same rule applies to income received through a professional partnership provided the patients are those of some active member of the partnership and look to him as responsible for the services performed. Min. 3802, IX-1 Cum. Bull. 121 (1930). See also G. C. M. 9716, X-2 Cum. Bull. 304 (1931). The income of a physician from his practice was held to be income from a trade or business under the 1917 excess profits tax which was applicable to individuals. A. R. M. 40, 2 Cum. Bull. 266 (1920).

tion if he is confronted with a serious or complicated illness. It is also a field in which highly trained advice is eminently desirable. Most doctors doubtless know members of their own profession to whose ministrations they would not want to submit themselves, and lawyers cannot be regarded as fungible, either. Finally, it may be fairly said that the field of trusts and taxes is full of uncertainties which only an expert can keep within his grasp, and the best he can do often is to guess. In about three-fourths of the cases, the best advice that can (and will) be given is, Don't.

There is one thing that a married man can do if he has full confidence in his wife, or is willing to take the chance that she may run off with money he may give her. If the doctor has made some accumulation from his profession, and has invested this in securities, the income from the securities included in his income and is in effect taxed in his highest bracket. If his total income is above the bottom bracket of surtax, he may save income tax (under the law as it stands today) by transferring the securities to his wife. Then the income from the securities will be taxable to her and in the lower brackets if she has no other income.³⁵ The gift will be subject to gift tax that exceeds the annual exemption of \$3,000 a year, or the general exemption of \$30,000. And it must be clearly understood that an outright unqualified gift to the wife is required. There must be no reservations or strings or understandings of any sort. The transfer will also have the effect of taking property out of the husband's taxable estate at the time of his death (unless the gift is found to have been made in contemplation of death). But the property will be taxable in the wife's estate on her death, and the husband may have to pay tax then to get his property back. And of course, the income tax saving would be lost if the Treasury should be successful in its efforts to have compulsory joint returns of the income of husband and wife, but so far Congress has consistently rejected that attempt.

SPECIAL PROBLEMS

There are several special situations dealt with in the law which seem worthy of mention, and which may occasionally arise in connection with a doctor's tax returns. The first two of these to be dealt with relate to the problem of allocating income to a proper period for the purpose of computing the tax payable.

Income Accrued at Date of Death When a doctor in active practice dies he will ordinarily have a substantial amount of fees due to him for work he has done but for which he has not received payment during his lifetime.

³⁵ Such a transfer is unnecessary in the eight community property states (Washington, Idaho, California, Nevada, Arizona, New Mexico, Texas, and Louisiana, and optionally in Oklahoma). In those states the income of a doctor from his profession is community property, and is taxable half to him and half to his wife. This results in a substantial discrimination in favor of taxpayers in these states, which would not be tolerated by the residents of other states, if they were fully aware of it. But to date determined efforts to eliminate this unfair arrangement have always fallen before the solid phalanx of sixteen Senators from the community property states.

This is a situation which is not peculiar to doctors, but applies also to lawyers, architects, insurance men, and many others. The items represent assets of the estate of the person who has performed the services. The question is then presented as to how they should be treated whether they are eventually collected by the executor after the decedent's death. In some early cases it was held that the amounts collected by the executor were not income to the estate, since they were merely the collection of the estate's assets, in the form of debts due to the estate. This led the Treasury in 1935 to secure the adoption of a clause in the statute which provided that all such items earned but not collected at death should be included as income of the taxpayer for the period ending with his death.³⁶ In other words they were treated as having accrued at the date of death, and the taxpayer was put on the accrual basis with respect to these items. In due course, this provision was sustained by the Supreme Court, and it was held that the items which must be included included the fair value of all services performed whether they had been billed or not.³⁷ With the rapid increase in tax rates in the following years this provision became very unfair, for it resulted in throwing into the income of the final return items of income which might have been spread over a period of several years. As the rates are sharply graduated, this caused a much greater tax than would have been the case if the tax had been spread over a period of several years. This tax would materially reduce the amount which a man in active professional practice could count on leaving for his dependents, since the tax would be a heavy liability against his estate at the time of his death.

Fortunately this difficulty was remedied by Congress in the Revenue Act of 1942. That statute adds a new section to the Code,³⁸ which makes such income taxable to the person who actually collects it after the decedent's death, less an allowance for the estate tax which may have been paid on account of the claim being included as an asset of the decedent's estate at death. This amendment was made retroactive, so that the pyramided tax may be eliminated in the case of any professional person who died before the recent amendment was passed.

Income Earned over a Period of More than 36 Months. Sometimes work is performed over a long period of time, and payment for the service is not received until at or after the close of the period. Very likely it happens to lawyers and others more often than it does to doctors, but there must be many cases in which doctors have to wait more than three years for a fee while performing services during the period. If the fee, when received, is substantial, the tax may be very much greater if it is taxed in full in one period than would have been the case if the fee had been divided up and paid equally during each year in the period, for the tax on a sum received

³⁶ Sec. 42(a) of the Revenue Act of 1934, continued into § 42(a) of the Internal Revenue Code.

³⁷ *Hickman v. Estate of Furrh*, 312 U. S. 636 (1941).

³⁸ Sec. 126. The previous provision in § 42(1) was eliminated.

in each of three years is less than the tax on three times the sum received all in one year. This is the result of the sharply graduated rates of taxation.

This difficulty has been alleviated to some extent by a provision included in Section 107 of the Code. Under this section, where at least 80 per cent of the total compensation for personal services covering a period of 36 months or more is received in one taxable year, then the amount so received may be treated for tax purposes as if it had been received ratably over the entire period. In this way the amount received may be spread over the three or more years involved and the total tax due with respect to it shall not exceed the aggregate of the taxes which would have been due if the proportionate amount of the total compensation had been included in each of the years of the period. This is a complicated provision, but it is a fair one. Many of the complications in the tax laws result from efforts of Congress and the taxing authorities to be fair. And the use of this section may save a substantial amount of tax in the occasional case where it is applicable.

Victory Tax The Revenue Act of 1942 includes a new tax known as the Victory tax. This has given rise to a good deal of confusion, chiefly because of the provisions which it includes for collecting the tax at the source from wages and salaries. Because the tax is withheld only from salary and wage income, the impression has sometimes arisen that only wages and salaries are subject to the tax. Specifically, some doctors have thought that their fees were not subject to the Victory tax. This impression is, however, quite unfounded. The Victory tax is applicable to all taxable income received by any taxpayer, whether derived from salaries, wages, fees, commissions, dividends, interest, rent, or any other source except capital gains. The tax is collected in advance, it is true, only from salaries and wages. But this is merely a collection device. All taxpayers will make a report of Victory tax when they file their returns on March 15, 1944. To the extent that the tax has been collected at the source from salaries and wages, the amount so collected will be a credit against the Victory tax due. But in the case of taxpayers whose income has not been subjected to collection at the source, the entire amount of the Victory tax will be due at that time.

A portion of the Victory tax is in effect a compulsory loan to the Government to be returned after the close of the war. In the case of single persons, this is 25 per cent of the tax, not to exceed \$500, and for married persons, it is 40 per cent of the tax, not to exceed \$1,000. An additional credit of 2 per cent (limited to \$100) is allowed for each dependent. This post-war credit may in effect be taken in advance, because amounts invested in war bonds, or used to pay off debts, or paid on life insurance premiums may be deducted from the tax at the time the return is filed up to the amount of the credit. If this is done the credit is of course reduced by the amount deducted.

If the doctor has employees of any sort, whether office or professional, required to act as a withholding agent and deduct the Victory tax from

the wages or other compensation which he pays (Withholding is not required from the wages of domestic or agricultural employees) The amount to be deducted is 5 per cent of all of the compensation in excess of \$12 a week The employer is personally liable for the amount of the tax withheld from his employees, and must pay it with a return on the proper form to his local Collector of Internal Revenue after the close of each quarter of the year The employer must also furnish to each employee after the close of each year (or after the termination of employment) a receipt for the tax withheld on a form prescribed by the Commissioner of Internal Revenue This is the form which the employee then files with his tax return so that he may secure credit against the Victory tax for the amounts which the employer has paid in advance on his behalf through the withholding collections

Men in the Armed Services The salaries of army officers are subject to tax just the same as other income, including the Victory tax (although there is no collection at the source of Victory tax from military and naval personnel on active duty) There has grown up a rule, however, under which the allowances of army and navy officers for quarters, as distinguished from their pay, are not subject to income tax³⁹ This arises from the difficulty of drawing a distinction between cases where quarters are furnished primarily for the benefit of the Government and the much more frequent situation where an allowance is made in lieu of quarters It crept into the regulations when tax rates were low and it did not make very much difference Under present conditions it results in a very considerable saving of tax, since taxpayers outside of the military forces have to pay full tax on that part of their incomes which they use to cover their rent, food and other living costs It is thus an indirect increase in the compensation of army and navy officers, which may well be fully warranted, but would be better done directly

Although an army or navy officer remains fully liable for income tax and Victory tax, the law allows him to defer the payment of any tax falling due during his period of military service if his "ability to pay such tax is materially impaired by reason of such service"⁴⁰ This deferment extends until six months after the termination of military service, and no interest is due for the period of deferment, and no penalty may be collected for non-payment The statute of limitations is, however, kept open for the period of deferment and for nine months thereafter Deferment in such cases is not automatic, but may be had on application and a proper showing to the Collector of Internal Revenue A similar deferment is now given in effect to any person, whether in the armed forces or not, who for more than ninety days "is continuously outside the Americas"⁴¹

³⁹ Sec. 1922(a)-3 of Regulations 103 "The value of quarters furnished to the commissioned officers, chief warrant officers, warrant officers, and enlisted personnel of the Army, Navy, Coast Guard, Coast and Geodetic Survey, and Public Health Service, or amounts received by them as commutation of quarters, are to be excluded from gross income."

⁴⁰ Sec. 513 of the Soldiers' and Sailors' Civil Relief Act of 1940, 54 Stat. 1178, 1190

⁴¹ Sec. 3804 of the Internal Revenue Code, added by the Revenue Act of 1942

QUESTIONS CONNECTED WITH THE PATIENT'S TAXES WHICH MAY BE OF INTEREST TO DOCTORS

The doctor is, of course, primarily interested in his own taxes. When tax rates were low and exemptions were high, there could be very few situations where the patient's tax bill could seriously interfere with the patient's obtaining proper treatment or with the doctor's being paid. Where tax rates are higher, however, the taxpayer would in effect get a substantial rebate against his medical expenses if they could be deducted, and this might have some effect on the doctor's collections. But with one important exception to be noted later, it is quite clear that medical costs are personal expenses and are not deductible in the ordinary case.

Where medical or related work has some connection with the taxpayer's trade or business, it has been occasionally argued that the cost could be deducted. In one case, a deduction was allowed to an actor for the cost of dental work required to replace teeth knocked out in making a prize fight picture.⁴² But generally such deductions have been denied. An early ruling refused to allow the deduction by a professional singer of amounts paid to a throat specialist for throat treatments.⁴³ The Board of Tax Appeals refused to allow a motion picture actress to deduct the cost of a tonsillectomy although she contended that it was necessary for the improvement of her voice.⁴⁴ In another case an actor and radio performer was denied a deduction of the sum of \$3,500 paid for new artificial dentures, although he claimed that the new teeth were necessary to eliminate a lisp and restore perfect enunciation which was required in the conduct of his work.⁴⁵ A lawyer sought to vary the claim by contending that the substantial expense of caring for his arthritis was deductible as a "loss" or as a damage by "casualty", but he was unsuccessful.⁴⁶

Certainly, ordinary medical bills would seem to be a clear case of "Personal, family, and living expenses," which are not deductible. But the doctor is familiar with many cases where there is a medical catastrophe, with hospital and other costs which are overwhelming even to a family which is ordinarily able to pay its way. It does not require imagination to picture a case where the family income is, say, \$4,000 a year, and an accident or illness to a child or other member of the family results in costs aggregating the entire family income of \$4,000. In such a case, it is rather harsh to tell the taxpayer that he must not only find a way to pay his ordinary living expenses, and the medical bills, but also a sizeable amount for income tax as well. He will find it hard to feel that he has had income when he has finished the year at a substantial loss through no fault of his own.

⁴² *Reginald Denny*, 33 BTA 738 (1935). The Commissioner of Internal Revenue has refused to acquiesce in this decision. XV-1 Cum Bull 30 (1936).

⁴³ O D 1032, 5 Cum Bull 172 (1921).

⁴⁴ *Madge Evans*, Memo BTA decision, March 8 1939.

⁴⁵ *Sparkman v Commissioner*, 112 F (2d) 774 (C.C.A. 9th, 1940).

⁴⁶ *Bourne v Commissioner*, 23 BTA 1288 (1931), aff'd, 62 F (2d) 648 (C.C. 1st, 1933), certiorari denied, 290 U S 650 (1933).

Recognizing the reality of this situation, and its impact at the present high tax rates, Congress has undertaken to meet it by a new provision in the Revenue Act of 1942.⁴⁷ This allows the deduction of what may be called extraordinary medical expenses. Specifically, it is a deduction for that part of the expenses of medical care which exceeds 5 per cent of the taxpayer's net income. Anything less than 5 per cent is treated as an ordinary personal expense, but medical expenses larger than that are deductible. There is, however, a top limit on the amount which may be deducted of \$2,500 for a married couple or the head of a family, and \$1,250 for a single person. "Medical care" is defined for this purpose as including "amounts paid for the diagnosis, cure, mitigation, treatment, or prevention of disease, or for the purpose of affecting any structure or function of the body."

This deduction should be of real benefit to many persons who are confronted with heavy medical expenses. There will doubtless be attempts to abuse it by persons who seek to deduct the costs of their annual vacations in Florida on the ground that their health requires it or that their doctor has ordered it. But most of the claims will be legitimate, and the relief afforded will be a real contribution to the problem of the costs of medical care.

PROCEDURE

Income tax returns are due the fifteenth day of the third month after the close of the taxable year. Most individuals make their returns on the basis of a calendar year, and their returns are thus due on March 15. But returns can be made on the basis of a fiscal year ending on the last day of any month,⁴⁸ and in some cases it is desirable to use a fiscal year. The return must be filed with the Collector of Internal Revenue for the district in which the taxpayer resides or has his principal place of business. Formerly the return had to be made under oath, but this was changed by the Revenue Act of 1942, and they may now be filed with a simple signature under the statement printed on the return form that the signing is made under the penalties of perjury.⁴⁹ The tax may be paid in full at the time the return is filed, or it may be paid in quarterly installments, the first paid with the return, and the rest at three month intervals thereafter.⁵⁰

In addition to the return of taxable income, each person must file an information return disclosing the amount and payee of all payments made in the amount of \$500 or more in any taxable year.⁵¹ (In the case of payments

⁴⁷ Sec. 23(a) of the Code added by § 127(a) of the Revenue Act of 1942.

⁴⁸ Sec. 48 of the Code. But the taxpayer cannot change from one accounting period to another without the approval of the Commissioner of Internal Revenue. Secs. 46 and 47 of the Code.

⁴⁹ Sec. 51 of the Code.

⁵⁰ A discount for advance payment may in effect be obtained through the purchase of Treasury Tax Savings Notes. These may be bought at any time, by reserving a portion of current earnings, for instance, and may then be used for the payment of subsequent income tax. They return interest of 16 cents a month on each \$100, or 192 per cent a year, on amounts up to \$5,000 a year. They may be purchased direct from any Federal Reserve Bank, or through the taxpayer's own local bank.

⁵¹ Sec. 147 of the Code.

made to employees from which Victory tax has been withheld, the receipt furnished to the employee takes the place of the information return) Information returns must be filed with the Commissioner of Internal Revenue in Washington, and are due by February 15 of each year Patients and others making payments to physicians of amounts of \$500 or more in any calendar year are likewise required to file information returns,⁵² so that the Government has a record of any such items in a medical man's income Thus may be some incentive against carelessness in making out a tax return

Once the tax return has been filed, it is checked and examined by the revenue authorities In many cases it is accepted as correct and nothing more is heard of it by the taxpayer In other cases, however, there are two possibilities The taxpayer may have paid too much, or the Government may think that he has paid too little If the taxpayer thinks that he has paid too much, either because he has included something in income which was not properly taxable as income, or because he has not taken a deduction to which he was entitled, he may file a Claim for Refund with his local Collector of Internal Revenue This Claim must be on a blank known as Form 843, obtainable from any Collector's office, and it must state the grounds on which the Claim is based The Claim cannot be considered unless it is filed within three years from the due date of the return (or within two years after the tax was paid, in case the payment was delayed for some reason) ⁵³ After the Claim is filed, it will be considered by the revenue authorities, and may be allowed If it is allowed, the overpayment of tax is refunded with interest at the rate of 6 per cent If it is denied, then the taxpayer's only alternative (unless he can get a reconsideration of the claim, and that is unlikely) is to bring suit in the appropriate court The suit must be brought within two years from the date of denial of the claim ⁵⁴ It may also be brought at any time more than six months after the time of filing the claim, even though the Commissioner has not acted on it

Probably the more frequent event is that the revenue officers have some question about the return In that event, they usually write to the taxpayer and ask him to come in with such records as he may have In many cases a simple interview is all that is required There may be some ambiguity on the return which is easily and satisfactorily explained, or the revenue officer may be seeking substantiation of some item claimed as a deduction If the explanations are not satisfactory to the revenue officer, however, he writes another letter to the taxpayer in which he says that he proposes to find that there is a deficiency in the tax payment, and the taxpayer is given formal opportunity to protest this finding if he feels that he has reason to do so, and so desires If the matter is not then satisfactorily

⁵² Sec. 19147-1 of Regulations 103 " Fees for professional service paid to attorneys, physicians, and members of other professions come within the meaning of the term 'fixed or determinable income' [in § 147 of the Code] and are required to be reported in returns of information as required by this section "

⁵³ Sec. 322 of the Code

⁵⁴ Sec. 3772(a) (2) of the Code

adjusted, the Commissioner's staff sends the taxpayer a formal determination of a deficiency.⁵⁵ The taxpayer may then either pay the tax determined, or within 90 days he may file a petition with the Tax Court of the United States seeking a redetermination of the Commissioner's ruling. From the decision of the Tax Court, either side may appeal to the higher Federal courts.

Whenever it is finally determined that the taxpayer owes an additional tax, the Collector's remedies for collection are very powerful and summary. He does not need to obtain any process from a court. After giving 10 days' notice, he has authority to distrain (that is, to seize) any property of the taxpayer, including bank accounts and any other assets,⁵⁶ and with the most meager and antiquated exemptions.⁵⁷ It should also be pointed out that any deficiencies in tax must be paid with interest at the rate of 6 per cent.

PENALTIES

Civil Penalties The tax laws work fairly smoothly when they are fully and fairly complied with. But they contain rather harsh provisions which come into operation when there is serious default in meeting the obligations of the statute. The mildest of these take the form of civil penalties which can be asserted and collected in the regular proceeding for the collection of the tax. The first of these is applicable to the failure to file a return on time. If the return is not filed when it is due, a penalty may be assessed of 5 per cent for each 30 days (or portion of 30 days) that the return is late, up to a maximum penalty of 25 per cent.⁵⁸ Even though a return is properly filed, a penalty of 5 per cent may be collected where there is a deficiency in the tax shown due on the return, and any part of the deficiency "is due to negligence, or intentional disregard of rules and regulations but without intent to defraud."⁵⁹ The major penalty, however, is the 50 per cent fraud penalty. This is due "If any part of any deficiency is due to fraud with intent to evade tax."⁶⁰ With tax rates where they are now, this penalty may impose a very severe burden. In one leading case,⁶¹ the Supreme Court sustained a fraud penalty in the amount of \$364,354.92 determined against a taxpayer,

⁵⁵ In the ordinary case, this notice must be sent within three years from the due date of the return. But if there is an omission of items amounting to 25 per cent of the gross income, then the notice may be sent within five years. And if the return is false and fraudulent, there is no time limitation on the determination and collection of the tax. Secs. 275 and 276 of the Code.

⁵⁶ Sec. 3690 of the Code.

⁵⁷ The exemptions allowed by § 3691(a) include arms for personal use, one cow, two hogs, five sheep and wool thereof, household furniture to an amount of \$300, and the "books, tools, or implements of a trade or profession, to an amount not greater than \$100."

⁵⁸ Sec. 291(a) of the Code. The Commissioner has power to relieve against this penalty where "it is shown that such failure is due to reasonable cause and is not due to willful neglect." This takes care of the situation where the failure to file the return is due to the taxpayer's illness or other disability. The penalty is of course not due where the failure to file return is during a period of military service or while the taxpayer is "outside the Americas," as indicated in notes 40 and 41 above.

⁵⁹ Sec. 293(a) of the Code.

⁶⁰ Sec. 293(b) of the Code.

⁶¹ *Hekman v. Mitchell*, 303 U. S. 391 (1938).

although the taxpayer had previously been acquitted by a jury of the criminal charge of filing a false return

Criminal Prosecutions In addition to the civil penalties, the Government may also proceed by way of criminal prosecution. Any person who willfully fails to pay a tax, file a return, keep proper records, or supply information may be found guilty of a misdemeanor, and subjected to a fine up to \$10,000 and imprisonment for not more than one year⁶². The penalty may be even more serious when a person "willfully attempts in any manner to evade or defeat any tax"⁶³. That is a felony, and may be punished by a fine of \$10,000 and imprisonment up to five years. Similarly, any person "who willfully makes and subscribes a return which he does not believe to be true as to every material matter" is guilty of a felony and may be subjected to the penalties prescribed for the crime of perjury⁶⁴.

These provisions have been the downfall of many characters of notoriety⁶⁵. They have also been applied a good many times in the cases of less prominent personalities, enough times to show the wisdom of playing square with the tax collector, even if a man cannot say with Justice Holmes that he likes to pay taxes. The Justice said that he liked to pay taxes, because that was the way he bought civilization, and there has never been a time when that was more true than now. The opinion has been held by some that tax evasion is not unknown in the medical profession, because it may be thought to be easier to get away with there than in some other fields of activity. Doctors usually receive their fees from many persons in relatively small amounts, and if a doctor is not honest, he may think that he can keep two sets of books, and return only part of the checks as income, or he may omit to return some or all of the cash fees that he receives, figuring that there will be no way to check up on them.

Admittedly, such action can impose a difficult problem on the tax collecting officers. However, it has been solved, more than once, and an example may prove of interest. In the case of *Wiggins v United States*,⁶⁶ the defendant was a dental surgeon who had filed returns for two years showing income of \$18,000 and \$20,000, when in fact his income was over \$30,000 for each year. It appeared that the defendant had kept two sets of books, one a secret "true book," and another "false book." Only a portion of the fees was included in the latter, and only this portion was returned. The Government learned about this through anonymous telephone calls which turned out to come from the defendant's nurse and secretary who had had charge of his office and books for several years. The defendant put his

⁶² Sec. 145(a) of the Code. See *Spies v United States*, decided by the Supreme Court on January 11, 1943, where it was held that a willful failure to file a return without more, must be prosecuted as a misdemeanor under this clause, and not as a felony under § 145(b), referred to below.

⁶³ Sec. 145(b) of the Code.

⁶⁴ Sec. 145(c) of the Code.

⁶⁵ See for example the case of *Capone v United States* 51 F (2d) 609 (CCA 7th 1931), certiorari denied, 284 U S 669 (1931).

⁶⁶ 64 F (2d) 950 (C.C.A. 9th, 1933), certiorari denied, 290 U S 657 (1933).

trust in her, and eventually she turned him in. He received a substantial prison sentence.

ESTATE AND GIFT TAXES

Brief mention may be made of the estate and gift tax provisions, for any doctor may at least hope to become subject to these taxes. The federal estate tax now allows an exemption of \$60,000, but all property in excess of this is subject to fairly high and rapidly graduated rates of tax. The tax is imposed on the net estate, and as in the income tax, the net estate is determined by defining a gross estate against which certain deductions are allowed. The gross estate includes all the property which the decedent owns when he dies, including any dower or marital interest which his wife may take in his property. It also includes any property which he may have transferred during his life time, either in contemplation of his death, or where he has reserved a power or other interest in it. The amount of life insurance payable by reason of death is included in full in the gross estate where the decedent either paid the premiums or retained incidents of ownership in the policy, such as the right to borrow, or take the surrender value, or change the beneficiary.⁶⁷ The entire value of property held jointly by the decedent and his wife is also included, if the property came originally from the decedent himself.

Against this property included in the gross estate, there is allowed the exemption of \$60,000 and two principal deductions. All debts, including funeral and administration expenses, and the expenses of the last illness, may be deducted,⁶⁸ and a full deduction is likewise allowed for all gifts and bequests to charity. The only other deduction is of property which has previously been subjected to the estate tax within five years. The estate tax is in effect a periodic property levy, and the Government says that it should not be imposed oftener than once in five years.

Parallel with the estate tax is the gift tax. This applies to all gifts made while the taxpayer is living. There are two exemptions, one of \$30,000, and the other which allows a gift of \$3,000 each to be made to any persons every year. In this way, a taxpayer can over a period of time give away a

⁶⁷ If the doctor's wife has independent means, estate tax may be saved under the law as it stands at present if she takes out the insurance on his life and pays all the premiums and takes all the incidents of ownership in the policy with no rights given to him in any event. In such a case, the proceeds payable on his death will not be taxable in his estate, nor will they be taxable as income to the wife. If the wife should die first, however, the value of the policy would be an asset of her estate and subject to tax there if her estate exceeded the allowable exemptions and deductions. The premium payments must be paid wholly from the wife's own separate property. It will not do for the husband to give the wife the money to pay the premiums, for then they would be paid "indirectly" by him. It is probably sufficient, however, if the husband gives the wife property freely and with no strings attached, and she then uses the income from the property to pay the insurance premiums. This is most likely to be true when the gift to the wife is made wholly independently of any plan to use the income to pay insurance premiums.

⁶⁸ This includes the reasonable charges of a physician who may have attended the decedent. The bill for such services is a "claim against the estate" of the decedent and is thus deductible. See *Lucas v. Littauer*, 25 B.T.R. 21, 28 (1931).

substantial amount of property without incurring the gift tax. If his gifts exceed these exemptions, then the tax applies. It is imposed at graduated rates on the taxable gifts made since the gift tax went into effect in 1932. The rates are in general about three-fourths of those under the estate tax. There is thus a substantial inducement to make gifts in the case of wealthy persons, and this inducement has been rather freely accepted by many persons. There are others, however, who do not have to concern themselves very greatly with the gift tax. But the gift tax exemptions and the estate tax exemptions are steadily moving lower and lower, and these taxes may soon follow the income tax in being made applicable to a much larger group of taxpayers.

TRAUMATIC PSYCHOSES *

By LT COL FRANKLIN G EBAUGH,† M C, F A C P, *Dallas, Texas* and
MAJOR HENRY W BROSN,‡ M C, *New Orleans, Louisiana*

INTRODUCTION

IN this section will be discussed only the forensic problems pertinent to the psychoses due to direct head injury. In the official classification of the American Psychiatric Association these are known as (1) Traumatic delirium, (2) posttraumatic personality disorder (new diagnosis) or traumatic constitution (old diagnosis), and (3) posttraumatic mental deterioration (dementia) ^{10, 20, 41, 46, 66, 67}. These designations do not describe sharply defined entities, but only variable symptom-complexes with overlapping boundaries. The numerous relationships of head injury to other psychoses¹ and neuroses² will be presented in other sections of this book. The senior author

* Received for publication March 5, 1943

† Professor of Psychiatry, University of Colorado, on leave, Neuropsychiatric Consultant, VIII Service Command, AUS, Dallas, Texas

‡ Assistant Professor of Psychiatry, University of Chicago, Chief of NP Section, La Garde General Hospital, AUS New Orleans, Louisiana

¹ Psychoses are major personality disorganizations characterized by poor contact with or appreciation of reality, disturbed ethical and social relations, decreased ability in most cases to pursue a gainful occupation or maintain stable relationships, which may or may not be accompanied by signs of organic brain disease, defects of the intellectual functions, emotional deterioration or accessory symptoms such as hallucinations or delusions. The concept of psychosis is primarily of legal rather than of medical importance and usually carries with it both denotation and connotations of incompetence at law. Examples are schizophrenia, manic-depressive psychosis, psychosis with brain tumor, psychosis with mental deficiency, psychosis with cerebral arteriosclerosis, psychosis with epileptic deterioration or epileptic clouded states, psychoses with psychopathic personality. Many individuals with a mild grade of these disorders may escape adjudication if they do not attract legal or medical attention.

² Neuroses are "minor" personality maladaptations, which may be severe but do not disrupt the individual's relations with reality (temporal, spatial, social, economic, ethical) sufficiently to cause him to be adjudged insane at law. The neuroses are types of adaptation and defense against inner conflicts, often largely unconscious, which have their origins in childhood, and are modified by subsequent experiences so that their natural history is the unique and individual biography of the person afflicted. They may be regarded as energy systems operating analogously to the simpler systems in physics. Here also are found indestructibility of energy, action and reactions in equivalent amounts, and the tendency of every energy system to seek an equilibrium (Second Law of Thermodynamics). Instinctual forces repressed by social training cause internal stresses which express themselves variously somatically, psychologically, socially. (A) *Somatically* neuroses may cause such disorders of the gastrointestinal system as vomiting, constipation, diarrhea and "colitis," bowel distress, belching, flatus, starvation (anorexia), over-eating, peptic ulcer, disorders of the cardiovascular system such as palpitation, tachycardia (fast pulse rate), pain in the chest, high blood pressure, suffocation, choking or labored breathing with attacks of acute anxiety, paleness, fainting, perspiration; disorders of the respiratory system such as some types of bronchial asthma, and difficult and irregular respiration both as to rate and depth, disorders of the skin with various types of wheals and eczema. Gross motor disturbances also occur as tremors, twitching (tics), paralysis of the hands, arms, legs, vocal cords, neck muscles, occupational cramps, lump in the throat (globus). Sensory disorders may be partial or total anesthetics which fail to conform to anatomic patterns but do correspond to glove or stocking type of distribution. The genito-urinary system may be affected by the neuroses in such a way as to manifest backache, impotence or premature ejaculation, amenorrhea, dysmenorrhea, urinary frequency or urgency, pain or discomfort in the pelvic region.

(Franklin G Ebaugh) has previously discussed them in another publication¹⁸ (See Chart A)

The growing interest in these psychoses is reflected in increased publication because of increasing economic value, greater prevalence, and better diagnosis. As an example of greater prevalence than is commonly known, we cite the fact that although less than 1 per cent of state hospital admissions are diagnosed as traumatic psychoses, yet Allen, Moore, and Daly³ found the surprising number of 245 (7.9 per cent) cases of subdural hematoma³ out of 3100 consecutive autopsies on psychotic patients.

Since more traumatic psychoses are being detected, inevitably the legal burden associated with most of them is increased. It is therefore worthwhile to present the better current psychological means of diagnosis, together with the possibilities for future improvement which will be of genuine aid to patient, attorney and physician. Until recently we were almost totally dependent upon physical means (skull roentgenograms, encephalograms,⁴ ventriculograms,⁵ subdural pneumograms,⁶ electroencephalograms,⁷ spinal fluid studies,⁸ and exploratory surgery)^{49, 51, 58a, 68b} to supplement the clinical ex-

Headaches of many types, dizziness, nausea, blurring of vision, ringing of the ears, weakness, fainting, lack of ability to tolerate heat, exposure, exercise or alcohol may all be caused by neurosis, as these same symptoms are frequently found in traumatic psychoses the problem of differentiation may be difficult unless physical findings, the life history, or special psychological tests aid materially in the diagnosis. (B) Psychologically neuroses may manifest themselves in a multifariousness of anxieties, projections, fears (phobias), obsessions, tensions, preoccupations, unusual marked interests, inhibitions of thinking, lapses of memory. (C) Socially neuroses manifest themselves in more or less frank patterns of sadomasochistic behavior, exhibitionism in more or less sublimated form, marked penury, avariciousness, meticulousness, irresponsibility, hostility, passivity, or pathological generosity, litigiousness, dependency, aggressiveness. Alcoholism, perversions, vagrancy, and other similar behavior patterns may be methods of defense against the anxiety caused by repressed conflicts.

³ A bloodclot beneath the tough outer casing of the brain next to the skull.

⁴ A roentgenogram of the skull made after the injection of air or gas into the spinal canal thus revealing some of the inner architecture of the brain. Distortions and abnormalities seen on these roentgenograms make possible better diagnoses of pathological conditions.

⁵ A roentgenogram of the skull made after the injection of air or gas directly in the drainage system (ventricles) of the inner brain through a small burr hole in the skull.

⁶ Injection of air under the dura (the tough outer casing of the brain).

⁷ An electroencephalogram is a graphic record on a paper strip resembling stockbroker's tape which records the "brain waves" from several areas of the skull. No operation required. It may reveal the presence of a bloodclot, tumor, or abscess in the brain. It is also useful for detection of convulsive states (epilepsy).

⁸ Spinal fluid studies usually include investigation of the cell count, the presence of globulin, the total quantity of protein, the Wassermann or Kahn reaction for syphilis, and the Lange colloidal gold sol reaction for detection of neurosyphilis or other disease of the brain. While drawing the spinal fluid from a needle inserted into the spinal canal between the third and fourth lumbar vertebrae, the fluid pressure is carefully measured by a water or mercury manometer. Pressures above 150 mm of water (12 mm Hg), a cell count over 8-10, the presence of globulin, total protein values above 40 mg per 100 c.c. are to be regarded as suspicious of an organic disease of the brain. Standard laboratory texts should be consulted for interpretation of these findings, for the normal range is often wide and marked increase must be noted before the findings can be used as conclusive evidence. The presence of blood in the spinal fluid after an injury is presumptive evidence of injury to the brain, in fact, more probable evidence than the visualization on a roentgenogram of a small linear fracture, hence it is desirable that all patients have one soon after the injury provided there are no medical contraindications. Positive spinal fluid findings six or more months after an injury are usually accepted as evidence of gross damage to the cortex whatever the cause may be.

aminations, for the psychological tests of the mental status were not sufficiently developed to be generally useful in a court-room. The test methods presented here are believed to be the best available for the psychological study of the traumatic psychosis. By their means organic "deterioration" or "incompetence" can often be demonstrated when ordinary lay observation or physical means fail. They meet the challenge that "the frontal lobes are silent" for they provide means to listen if one is willing to pay the price.

*If specific tests designed for testing limited functions are utilized by experts, damage can be demonstrated long after the clinical picture is one of apparently good recovery*¹¹. We are on the threshold of new methods for studying and appraising alleged "traumatic psychosis," and it is one of the purposes of this paper to present the types of examinations which courts may well expect competent psychiatrists to make in this group of cases before bearing witness in court.

I PSYCHOSES DUE TO HEAD INJURY

A TRAUMATIC DELIRIUM

1. *Symptomatology* Traumatic delirium is usually characterized by a disordered sensorium (defective attention and awareness, impaired reception and synthesis of sensory impressions, often giving rise to misinterpretations especially in the auditory and visual spheres), a generalized haziness or confusion, motor restlessness,⁹ perhaps with excitement and wandering, and lack of motor control, defective immediate and remote memory, the loss of social, temporal and spatial orientation, including a phasic periodic failure to recognize even common or familiar places and persons, a tendency to spontaneous verbal productions, often expressing imaginative figments, which may or may not be coherent^{6, 10, 27, 40, 66, 67, 72}. Hallucinations, usually visual, are not uncommon. The pervading affect is usually tinged with apprehensiveness or fear. Among the character traits one or more of which may appear prominently, are belligerence, aggressiveness, demandingness, depression, passivity, suspiciousness. Irritability and uncooperativeness are quite common.

2. *Prognosis and Legal Implications* A delirium is to be regarded as of the same degree of seriousness as a pronounced skull fracture or a prolonged coma,¹⁰ for the underlying causes are the same (concussion,¹¹ contusion,¹² laceration,¹³ hemorrhage and increased intracranial pressure). The terminal behavior disorder resulting from these lesions may be more widespread than is usually accepted^{1, 2, 3, 22, 26, 29, 41, 59, 60, 62, 64, 68, 77}. These healing processes may be relatively unattended by pain, dizziness, unsteadiness, syncope¹⁴ or convulsions yet be sufficiently extensive to alter the cere-

⁹ Irregular movements, usually aimless, of the arms, legs, or body.

¹⁰ A coma is a state of profound insensibility.

¹¹ A concussion is a state of unconsciousness caused by mechanical displacement of brain tissue usually associated with direct local injury and tears.

¹² A contusion is a bruise or disorganization of tissue usually accompanied by bleeding.

¹³ A laceration is a tear or break in the continuity of the tissue structure.

¹⁴ Syncope: fainting.

bral functions in the same manner as other lesions causing loss of cerebral tissue. It is possible that the phagocytic¹⁵ cells may attack "uninjured brain tissue"⁴⁶. Of more than passing interest is the belief that the disturbed circulation and hence the nutrition and metabolism may be important factors in the recovery from head injury^{28, 52, 54}. Powell⁵² cites evidence that poor nutrition, prolonged hypotension¹⁶ and prolonged increased intracranial pressure may be operative in many diseases.

(a) Relation of duration to prognosis. The prognostic signs may be of legal significance since they are quoted in order to establish the probable severity and outcome of a case. The presence or absence of a fracture is of little prognostic or diagnostic aid if there is no depressed fracture causing direct mechanical compression⁵⁵. Severe concussions without evidence of skull fracture cause deterioration as frequently as those with skull fracture^{17, 62}. Deliria of mild grade and under 24 hours' duration are usually followed by fairly good recovery, but the rule is far from invariable. Deliria of more than one week's duration suggest more profound damage and final estimates of the residual symptoms and destruction should not be made for at least six months when the re-organization of the brain tissue is stabilized. Delirium or unconsciousness of more than one month's duration almost certainly represents severe tissue destruction which requires a guarded prognosis. Final estimates should await stabilization, which may not occur for six to eighteen months. Some clinical judgment is necessary before permitting a patient to be examined psychologically for legal compensation purposes. The greatest damage will be apparent during the early months of convalescence before the powerful compensatory trends are fully established. A standard practice will probably be established regarding the optimal time for psychological testing as these methods are utilized more generally.

In the young recuperation is better, for traumatic psychosis will almost certainly not occur^{19, 62}. The presence of paranoid trends,¹⁸ persistence of symptoms for two years, or advancing age are prognostically unfavorable. It should be remembered that the prognosis may well be dependent upon the therapy in some cases for the best physiologic and psychiatric care may prevent many unfortunate sequelae.

The clinical courses of deliria vary widely, some of them persisting for several weeks. The latter often resemble the well known Korsakoff syn-

¹⁵ The "white" or scavenger cells of the blood or special cells in the brain which are mobilized in the presence of injured tissue.

¹⁶ Low blood pressure.

¹⁷ A fracture is a dissolution of the continuity of bone. When the bony fragments press directly against the brain it is called a depressed fracture.

¹⁸ Paranoid trends usually refer to ideas or delusions of persecution. They may be expansive in character and then the patient may believe himself to possess unusual strength, special, often magical abilities, or unusual powers (he becomes "an inventor," "Christ," "Napoleon"). Egocentricity, suspiciousness, and the propensity for placing blame on others together with seeing special "significance" or drawing inferences in otherwise neutral events distinguishes the paranoid character. Intelligent paranoid characters are notoriously excellent litigants, for their personality augments any native abilities in this direction. Naturally, with deterioration and loss of ethical considerations these litigious trends increase and are difficult to separate from legitimate demands.

drome¹⁹ (not to be confused with the "alcoholic" Korsakoff symptom-complex due to vitamin B₁ (thiamine) deficiency) Here are seen fabrications having more or less basis in fact, confabulations wherein the patient fills in gaps in memory, especially on direct questioning, with imaginary occurrences, usually in a fairly coherent form and with the appearance of verisimilitude Unconscious trends may be apparent in these fictions which may be useful to the therapist in the convalescent period

(b) Forensic implications of phasic deliria Occasionally the phasic character of a delirium becomes a major forensic problem, especially where disposition of property is concerned A will or money settlement made by a patient during a so-called "lucid interval" may seem to many to be an accurate expression of the patient's desires, but from what has been said about the basic pathology it is apparent that the fluctuation between "clearness" and "confusion" of the sensorium causes these terms to be only relative It seems certain that the tissue functions are severely disturbed if there are detectable signs of either neurological or psychological dysfunction Although the effects of the injury may be reversible with rest and healing, the physiological homeostasis²⁰ during the delirium is unsettled, and until a healthy balance is reestablished many psychological functions are impaired or entirely unavailable The patient cannot be said to be of "sound mind and sound body" when the integrity of the central nervous system is physiologically disrupted in a demonstrable manner, nor can it be said that the injured patient is at such time able to give due weight and consideration to all factors after mature reflection

This principle that the constancy of underlying etiology shall determine the fact of competence was apparently recognized by the United States Supreme Court when it decided that the jury should consider evidence that the defendant was intoxicated at the time of the crime in the case of *Hopt vs People* (104 U S 631) The incapacities caused by the toxic effects of alcohol are analogous to those caused by a head injury

To lay observers it is a shock to see demonstrated the many defects of the sensorium of a patient that had seemed to them to be lucid The persistent continuity of the underlying physiological disturbance must be understood in order to avoid the error of assuming a patient's competence upon superficial examination Halstead^{24b} cites the instance where intelligent business men, misled by an occasional thread of lucidity, repeatedly consulted a patient in a post-operative toxic delirium following removal of a left pre-frontal lobe tumor, on matters involving many thousands of dollars, when the patient was really confused, incontinent and seriously disoriented for time, place and person Only careful psychological examination can determine the relative integrity of the cerebral organization under these circumstances

¹⁹ A syndrome is a group of symptoms occurring together
²⁰ Homeostasis is a state of optimal equilibrium

Example of delirium with gradual recovery The patient is a 28-year-old single white male pharmacist. On November 28, 1942 the patient was thrown from his car as it failed to take a turn. He struck the pavement on the right side of his body, sustaining a fractured scapula, fractured ribs, and mild lacerations of the right frontal region of the skull. The patient was hospitalized in a short time, went into mild shock, but responded in several hours to the usual treatment. He remained unconscious for seven days. He was incontinent, restless, and from the first it was apparent that he moved the left arm and leg more than the right. He became aware of his surroundings very slowly. On making purposeful movements, it was evident that he had a right-sided hemiparesis with involvement of the third and seventh cranial nerves on the right. The spinal fluid was grossly bloody. The temperature rose to 102°, and after two weeks returned to normal, under management with codeine, paraldehyde, fluids and magnesium sulphate by nasal tube. Cheyne-Stokes respiration was present from the third to the fifth day following the injury. From the seventh to the twenty-eighth day following injury the patient's confusion and disorientation gradually cleared. He became more cognizant of his surroundings, his movements became better integrated, memory for events preceding the accident improved, but he was amnesic for a period of at least a month following the accident. Six weeks after the injury the patient's sensorium was clear except for occasional evidences of mild confusion. Recovery now uneventful with no residual symptoms. Impression: Cerebral contusion, subarachnoid hemorrhage, traumatic delirium, hemiparesis, right.

3 Differential Diagnosis A diagnostic problem of major legal importance is the differentiation between an organic delirium, hysterical symptoms in a "panic state," "hysterical delirium,"²¹ and frank malingering for compensation. The events leading up to an accident may be so frightening that the patient, although suffering little or no head injury, may be overcome by a "panic state," i.e. confusion due to extreme fear (see "traumatic neurosis"), which superficially resembles a delirium but is usually identifiable after close observation and response to therapy by an impartial specialist. More difficult is the recognition of a thorough-going "hysterical delirium" sometimes closely resembling one of toxic-organic origin, but differing from it in its susceptibility to resolution by such methods as reassurance with or without sedation, hypnosis, sodium amytal, interviews or physical shock. Outright malingering without a hysterical component is probably uncommon, and can be detected by a specialist in the course of a routine examination of the sensorium because the behavior is not appropriate to the situation. In one way or another the malingerer will overplay or underplay his act if the physician can take the time to give him an adequate stage on which to reveal himself.

Uremia as a complication of head injuries without damage to any other part of the body has not been generally recognized, but Cumings¹² of London in an investigation (1940-42) upon air raid casualties found chemical blood studies and autopsy proof that renal damage existed in some cases of head injury. The mechanism causing uremia following head injury or the

²¹ An hysterical delirium is a delirium (see definition under "Traumatic Delirium") due to hysteria.

renal lesions following traumatic anuria is unknown. Since uremia is often attended by confusion, disorientation or other signs of psychiatric nature it is important that this condition be looked for in order to institute proper treatment.

Another unusual condition which should be ruled out is acute pulmonary edema which may occur following injury and be accompanied by psychiatric symptoms. Weber and Blum⁷⁰ describe a man of 40 with a "screaming coma" who developed an acute pulmonary edema.

A standard but difficult problem in diagnosis is the evaluation of the alleged damage caused by a head injury in a patient who can be shown to have been suffering from hypomania before his accident, and who claims that his posttraumatic state is due solely to the accident. The standard articles by Ebaugh and Benjamin,¹³ Strauss and Savitsky,⁶⁶ Bowman and Blau⁸ and I. S. Wechsler⁷² are valuable references on this subject as well as on the question of traumatic precipitation of psychosis.

Example of Ma Fo The patient is a 56-year-old professional man who acquired an enviable prominence in his community by his energy and ability. He was restless, driving, "temperamental," with rapidly fluctuating moods throughout his life including several periods of depression. He suffered a head injury in 1938 from a diving accident without apparent sequelae. In February, 1942 he was forced to undertake new duties which made him obviously irritable, tense, distractible and uncooperative. Hypomania of mild degree was diagnosed in August, 1942 by a physician but the patient went on working. In November, 1942 he drove off the road in order to avoid a collision and was only, apparently, momentarily stunned. He claimed at first to be physically unhurt and there was no physical evidence of injury, but he did feel "shocked" and later ascribed his increased hyperactivity, increased pressure of speech, confusion and partial disorientation to the effects of the accident. He entered the hospital in a restless, disheveled state with circumstantial speech, flight of ideas, distractibility, preoccupation and short periods of confusion. Recovery occurred gradually with no evidence on various tests of any genuine cortical damage. It was held that he had no basis for a claim because of the previous personality history and absence of data to prove that a head injury had been sustained.

A complete amnesia²² for events following a head injury (anterograde type) is uncommon after the period of coma, stupor or delirium. Retrograde amnesia, i.e. that one screening the period before the accident, is more common than the anterograde, usually obscures only a short period before the accident, and is more diffuse and less complete than an hysterical amnesia. The latter may be so complete that the identity of the person is lost. Fiction writers have exploited this device so much that many persons assume that such loss of personal identity after head injury is common, whereas clinically complete amnesia, i.e. loss of memory for most of the facts of the patient's past life without aphasia,²³ actually occurs more characteristically in hysterical individuals who want to escape an undesirable life situation. Likewise, complete failure to recall the events before an accident occurs more fre-

²² Amnesia is memory loss.

²³ "Aphasia is the total or partial loss of the use or understanding of language, the vocal cords remaining intact." (Merriam Webster, 1933)

quently in persons with an hysterical personality who gain something by the amnesia. One example is that of a university student who became completely amnesic after an accident in which his fiancée was killed but whose memory was restored by hypnosis²⁴. It seems that he was ashamed to admit that they were parked on a railroad track and the consequent shock and guilt motivated an obliteration of the painful event.

4 *Factors Influencing Recovery* Although a prolonged delirium of many weeks' duration augurs poorly for restitution without damage, some patients make a splendid recovery because of their previously excellent character organization. In general, the form and content of the psychosis depends upon the personality of the individual patient^{17a}. Recovery certainly depends as much or more upon the strength and assets of the character than upon the relative severity of the injury^{18, 60, 72}. Of two men, each having approximately the same order of head injury, the one with the better integration will make much the better recovery. The fact that patients with apparently only a mild intellectual deterioration really have extensive cerebral damage suggests powerful psychological compensatory capacities. These capacities for regaining apparent normality furnish the basis for therapeutic optimism and the rationale for research methods to improve our knowledge of treating them. The prognosis then depends upon three factors: (1) the severity of the injury, including the site of injury and the amount of tissue damaged together with secondary physiological changes (shock, pressure, hemorrhage, nutrition), (2) the relative strength and viability²⁵ of the character organization, (3) the treatment regime which utilizes to the full the capacities which remain functional, increasing the field for the compensatory processes to act, teaching technics to improve common integrations, encouraging such latent creativities as may be substituted for the losses.

SUMMARY, SECTION I

A traumatic delirium is caused by tissue displacement or injury and characterized by many disturbances of the sensorium. These are best detected by psychological methods, when physical signs are absent. Although the delirium may appear to alternate with "lucid" states, it is often possible to show that important basic psychological functions remain impaired, so that it is important that no legal commitments be made until physiological stability is assured. The prognosis for ultimate recovery varies with the duration of this delirium, if all other factors are equal. Deliria of more than one month's duration seldom recover without patent residual damage. An outstanding factor for estimating potentiality for recovery is stability of the pre-traumatic character organization.

²⁴ Hypnosis is the induction of a state of narrowed consciousness, in which the subject is hypersuggestible to the hypnotist.

²⁵ Viability is the capacity to maintain integrity and resist dissolution.

B TRAUMATIC CONSTITUTION OR POSTTRAUMATIC PERSONALITY DISORDER

1 *Symptomatology* The name "traumatic constitution" or posttraumatic personality disorder is given to a variable symptom-complex to describe the poorly demarcated intermediate zone between head injuries recovering without apparent disability and the "posttraumatic mental deterioration" ^{27, 30, 41, 46, 58, 60, 67, 72, 77} The word constitution here refers to the psychological structure and not to the genetically determined physical structure of the patient. Usually this diagnosis is applied to fairly obvious changes in personality or character, some of which are accepted as being "caused" by head injury, together with newly acquired subjective symptoms, which may or may not be related to the head injury. Some months after an accident, perhaps on returning to the ordinary exertion of work, the patient and his associates notice that his energy level and work output are markedly lower, with serious decline of his attention, memory, and ability to sustain concentration on projects. These intellectual disorders and the important mood disturbances, to be described later, are often complicated by more or less severe headaches, usually unlocalized, or a sense of pressure in the head. Severe headaches are extremely painful and often of long duration. They are accentuated in degree and prolonged in duration by any exertion, excitement, or sensory stimulation, especially loud noises, bright lights, or heat. These patients are less tolerant of alcohol, heat, exertion, sunlight, some few drink to escape their pain. Dizziness, usually aggravated by sudden change of position, is another common symptom. Convulsions occur if the motor cortex ²⁶ is involved by scar formation, hemorrhage or pressure. Many types of character disorder are revealed, probably in susceptible individuals, of these, panic and rage and various hysterical states are the most common. These complaints have no apparent relation to the presence or absence of skull fracture or delirium. The sooner they occur after the accident the more probable is an etiological relationship; little credence is earned if they occur more than two years after the injury.

As the condition grows there becomes apparent gross retardation and impoverishment of thinking and speaking. Ideas, especially of the more abstract variety, are handled with less dexterity, fullness and speed, if handled at all. There is constriction of the psychological fields of interest, both immediate and remote, with little or no spontaneity, gaiety, originality or invention. Clinging to the comparative security of the concrete facts of everyday living, avoiding the unknown or changing conditions, adhering to the familiar and safe, there is made, apparently, a consistent effort to reach a safe, though dull, equilibrium. When this monotonous security is broken, the response may take the forms of restless anxiety, irritability, nagging.

²⁶ The motor cortex is the third frontal convolution of the brain just in front of the central fissure. All voluntary muscular activity results from impulse discharges from this area.

fault-finding, all in an effort to reestablish the cherished state of freedom from painful stimulation. If the stimulus is too painful or threatening to be controlled the result is the well-known fit of temper, a violent outburst combining rage, aggression and motor excitement. These "catastrophic reactions" ²⁰⁴ usually subside fairly quickly if the patient is permitted to sink back into his haven of seeming vacuity. Many patients avoid the anxiety of anticipation of the unexpected by keeping busy at many little familiar tasks ⁸⁵. Naturally such a patient will seem egotistical, self-centered, willful and selfish. Because so much of his energy must be diverted to avoid anxiety and pain, he has little energy left for free play of interest in, or love for his family, friends, business, hobbies. This fight against being hurt may well accentuate any tendencies to depression he may have, showing themselves in morose weeping, brooding self-pity, acrimonious guilt and recrimination. More and more he will learn to avoid exposure to unthinking persons who inadvertently strain his tolerance, or unwittingly force him to make gigantic efforts to retain his composure, that fine balance of emotional-intellectual forces which enables him to deal effectively with reality. If his social isolation becomes uncomfortable he may develop paranoid beliefs about those around him, as absolute strangers in a foreign land or partially deaf people are known to do. Others overcompensate for their inner weakness and insecurity by developing obnoxious aggressiveness, whereas the immature may regress quickly to infantile dependency, cleverly adapting technics to gain attention and affectionate care. Since this latter maneuvering is common to many invalids it may have a "non-specific" quality, i.e., almost anyone who is genuinely sick and dependent will show some tendency to regression along the road by which our character is built up. Similar processes are constantly at work in the neuroses, for the people so labelled are only those who have not attained a stable maturity out of the earlier developmental states because of their inner, often unrealized conflicts.

Case of Jc Po The patient is an 18-year-old farmer who sustained a severe head injury with unconsciousness of 5 hours' duration when hit by a passing automobile when he was eight years old. Family history is negative for epilepsy. He had been normal in behavior and school performance up to this time, but found school work increasingly difficult, so he quit at the age of twelve. His energy output, social and work interests decreased as he grew older. He had periodic headaches of four to eight hours' duration, apparently precipitated by exertion or heat. Poor tolerance of alcohol was present. During his fifteenth year he had a frank convulsion with tonic and clonic convulsions, incontinence, unconsciousness and a period of disorientation. No aura was reported. These convulsions recurred irregularly during the next two years, but he learned to avoid any situation which might precipitate them and did not have any for more than one year. No medical treatment was received during this time. A change of occupation requiring exertion and routine exposure to heat in his eighteenth year apparently caused recurrence of convulsions. The neurological and laboratory examinations, including roentgenograms of the head were consistently negative. This case is illustrative of numerous others in which headaches appear earlier and occur with greater frequency than convulsions. He also demonstrated on the ward and in special tests the types of defensiveness against noxious stimuli.

described above. Although ordinarily pleasant and cooperative when a request was made of him, he became tense and irritable if repeated demands were made of him, especially if the ward was noisy, and the directions given in a peremptory manner. He invented a routine for himself, took solitary walks, avoided activity in social groups, although he did like to talk to a few people. He wanted to do things but felt inadequate and, if pushed, became petulant and resentful. He was quickly downcast if refused minor requests. There was a pervading air of tension about him when he was active, which was relieved when he was able to sit alone. After one year's observation it is obvious that the prognosis is poor.

Case of J P The patient is a 23-year-old unmarried white male salesman who was kicked in the frontal region of the head by a horse on March 23, 1941. He was taken to a hospital immediately where he remained unconscious for about 36 hours, although he did arouse enough several times to talk to the nurses, but could not remember what was said. He was kept on bed rest for three weeks, but the first time he was allowed up he experienced a severe headache and blurred vision, with recurrence whenever he exerted himself, although he was free from symptoms for increasingly prolonged periods of time. On May 19, 1941, having been on a mild convalescent regime in the meantime, he arose from an afternoon rest period and fell unconscious after taking a few steps. There were no convulsions, and he regained consciousness after several minutes. At no time did repeated neurological or laboratory studies, including roentgenograms, or spinal fluid examination reveal organic disorder. On entrance into the hospital there was apparent slight bilateral edema of the optic nerve head and slight constriction of the left visual field which cleared up in two weeks. The headaches persisted during 341 days hospitalization occurring at variable intervals of 3 to 20 days with variable severity. There was a slow tendency to improvement, but exertion beyond his expanding tolerance was certain to precipitate an attack. Careful review of his past life history as obtained from his parents and friends revealed no definite evidence of overt neurosis. His work record had been good, and that in a field where alertness, energy, sociability was required. In the hospital he was apathetic or tense at intervals became quick to take offense and developed a temperamental sensitivity which was foreign to his previous character. He himself deplored his seeming preference for the empty activity of a hospital patient yet felt afraid to risk much activity because of the swift penalty of a headache. His former ambitions and pursuits were abandoned in order to spare himself pain. His mood was generally lowered with only occasional periods of cheerfulness. It was held that his present status was due to the injury and that he was eligible for compensation. Follow-up studies six and twelve months later revealed only mild improvement. Tests for abstract thinking seven and nine months after the onset revealed mild impairment.

2 Conditions to be differentiated from posttraumatic personality disorder Those unfortunate individuals whose post-accident personality is altered principally or totally by the emotional components are usually said to have "posttraumatic hysteria." Since this subject is featured in another article in this symposium, only a few comments will be made for the sake of completeness. The following diagnostic classification taken from Ebaugh and Benjamin¹² will illustrate the principal clinical subdivisions.

Traumatic personality disorder (traumatic constitution)

Simple type with subjective complaints of headaches, vertigo, irritability, fatigue, impairment of memory, etc.

With secondary psychogenic symptoms

With malingering

Posttraumatic functional disorders

Posttraumatic hysteria a true hysteria precipitated by trauma in an individual with an underlying neurotic personality May be accompanied by malingering

Compensation neurosis an hysteria in which the wish for compensation plays a leading rôle in the (unconscious) production of symptoms May be accompanied by malingering

Traumatic neurosis a neurosis usually hysteriform with pronounced anxiety features ("terror neurosis"), in which the psychogenic mechanisms differ from those in ordinary hysteria, and in which trauma may be considered as one of a series of true causative factors

Malingering

The posttraumatic hysterias and compensation neuroses are generally believed to be forms of hysteria,^{40, 67} although some authors^{13, 150 73a, 33b 37} are of the opinion that they are more akin to psychoses If they are genuine hysterical patterns, manifesting themselves in the special setting following an accident, it may be assumed that they are purposeful Usually this purpose is some type of gain money, "invalidism," escape from undesirable responsibility, domestic difficulties or a disliked job The important fact to remember, however, is that the patient with hysteria is unconscious of his true motives and insists quite honestly that he is suffering from a disability Sometimes the unconscious emotional gains quite outweigh the material advantages and hence are sometimes known as "primary" If therapeutic foresight were utilized quite early in the illness by means of judicious medical and legal advice, rapid legal settlement, lump sum payments, and early activation, many chronic sequelae could be avoided

The symptoms of posttraumatic hysteria may appear at any time after an accident Unfortunately these subjective complaints may occasionally mimic those of the organic cases headaches, dizziness, fainting, insomnia easy fatigue, difficulties in memory or concentration and the concomitant mood changes of anxiety, heightened irritability and depression If these symptoms appear more than six months after the accident they should be examined even more carefully than ever by prolonged observation, detailed pre-accident personality history, and special tests To an experienced clinician the hysteric's complaints seldom are of the same character as those of a true organic case When the hysterical complaints are those of functional paralyses, non-organic atypical anesthetics, hysterical gait or blindness the diagnosis is easy When the symptoms resemble those of a true organic case it is necessary to demonstrate the positive signs of a neurosis as well as negatively to rule out the presence of organic injury The diagnosis cannot be made by exclusion alone, hence it is imperative to show the past and present operation of hysterical mechanisms and character reactions

Traumatic neurosis

To clarify terminology, it should be stated that the concept of "traumatic neurosis" (a term originally used by Oppenheim to designate cases in which neither gross organic lesions nor true psychoneurotic mechanisms could be demonstrated) is used by Ebaugh and Benjamin,¹³ Wechsler⁷² and others for an acute anxiety state or panic reaction following such serious threats to life as occur in war, earthquakes, mining and sea disasters, but occur only rarely in ordinary automobile and industrial accidents. Strauss and Savitsky use the appropriate term "terror neurosis," a literal translation of the original designation of "schreckneurose" by Horn. Cases with severe head traumata seldom have this syndrome as a sequel, hence it is of little medico-legal importance in civilian life. They tend to clear up spontaneously, although characteristic dreams in which they relive the traumatic event repeatedly may persist.

Malingering

This bitterly contested topic is well discussed by Strauss and Savitsky⁶⁰ and I. S. Wechsler.⁷² Malingering is voluntary deception for gain, and may accompany minor injury or hysteria. Actually it is not very common.^{13, 72} The diagnosis is usually not difficult.

"Typical are gross inconsistencies in behavior and the production of mutually exclusive and contradictory symptom-complexes. The hysterical patient is really sick, no matter how "imaginary" his sufferings may seem to the layman, the hysteric is really unable to see, the malingerer, if he believes himself unobserved, will often betray himself in this respect. It requires extraordinary histrionic ability and presence of mind to mangle consistently over any length of time, and almost invariably the patient over-reaches himself in his efforts to convince the physician. Occasionally, however, prolonged observation is necessary. In any case, after the diagnosis of malingering as such has been made, the simultaneous existence of true posttraumatic organic or functional psycho-pathology must be excluded before we are justified in branding a patient as a pure malingerer, with the resultant total refusal of compensation."¹³

3 *Medical and legal concepts of "insanity"* Although the posttraumatic constitution or posttraumatic personality disorders are formally classed as traumatic psychoses, it may be well to mention that the medical and legal criteria of "sanity" are not identical. Medically, a patient is psychotic when palpable psychological damage is demonstrable, for if his judgment or insight is impaired at the basic levels of his functioning, it is unfair to him to be held responsible for acts which depend upon these fundamental functions. This does not mean that he cannot do a great many things very well, it only means that he may at any time do something wrong owing to the effects of the injury. With the development of secondary elaboration of his depression, aggressiveness, or paranoid trends he will, as a matter of course, be exposed to situations stimulating more anti-social behavior which may force him to be a litigant in some form.

4 *Organic and functional components of "traumatic" disorders* From the descriptions it is apparent that the interplay between "organic" deterioration and "emotional" defences make difficult any quasiquantitative estimation. Both emotional shock and brain tissue damage can motivate regression to less mature integrations and less efficient action patterns. If sufficiently concrete information can be obtained about the patient's past levels of efficiency by skilled impartial investigators, the task of estimating the loss of efficiency will be less arduous. Many cases could be easily resolved if the true picture of the pre-accident personality were available. The biggest aid in differentiation between "posttraumatic hysteria" and "traumatic constitution" on direct examination, without benefit of the past history, will be the demonstration in the latter group of the organic type of intellectual deterioration.

We have stressed the importance of evaluating the entire personality and behavior before and after the injury in making an evaluation of the damage incurred. Some authors, notably Kennedy,³⁰ believe that if headache and dizziness persist for more than four months in a man under 60 years of age they are to be regarded as neurotic symptoms, if the following seven criteria of head injury sufficient to produce organic changes in the brain are all absent—roentgen evidence of skull fracture, bloody spinal fluid, bleeding from skull orifices (especially from the ears), focal cerebral palsies, convulsive states proved to be posttraumatic, ventricular distortion proved to be posttraumatic, and a history of prolonged unconsciousness. It seems imperative that every physician testifying as a witness have available this evidence if it is possible to obtain it. "These criteria are of great value in giving a general orientation as to the probabilities in any case, but they seldom permit of a definite decision one way or the other without further examination. A history of prolonged unconsciousness is unquestionably of great importance, but many cases of head injury with such a history show no chronic mental or neurological sequelae, conversely, clinical, encephalographic and operative observations have proved that organic brain damage can be caused by head injury which was accompanied by unconsciousness of only a few minutes' duration or, rarely, by none at all. The same holds true, to an even greater degree, of skull fracture and bleeding from the ears. The other criteria mentioned are certainly strong presumptive evidence of organic brain damage, when they are present, their absence, however, does not exclude the possibility of such damage."³¹

In addition to the neurological and laboratory aids mentioned, every physician will want a thorough psychiatric examination comparing personality changes alleged to be present with the actual facts as elicited from impartial witnesses. The sensorium will be tested by careful and repeated examination of the retention and recall using pictures and objects as well as digits. Adaptations of Head's tests for aphasia are useful (a) naming and recognition of six or more common everyday objects, together with

reading the names of these objects on cards and writing the names and speaking them, (b) naming and recognition of color using eight colored silks as in (a), (c) testing elementary reading of very simple sentences, then asking patient to write very simple sentences, then asking patient to write them from memory and from dictation, (d) asking patient to tell the time from cardboard clock faces with movable hands and asking him to set them at stated times, (e) in succession the patient is asked orally, and by written command to place each of four coins in a saucer, (f) patient is asked to imitate movements made by the examiner's hand in pointing to his own ear or eye, the test can be varied having him imitate the movements of the examiner as reflected in a mirror; (g) the patient is asked to repeat the alphabet, days of the week, months of the year and various combinations. (h) the patient can be asked to read a paragraph and repeat its meaning, (i) graduated arithmetic tests, puzzles, drawings, and simple games are also valuable. Speed as well as accuracy should be recorded. The usual psychometric examinations (Binet, Terman, Bellevue) may show "scattering" of a degree and type which is more valuable than the formal test score. D. Wechsler's criteria for the organic syndrome will be discussed in this connection in Section III of this paper along with the more specific tests (Rorschach, Goldstein, Halstead, Shipley, Weigle, Kohs, Bolles, Kraepelin). Each physician will select those tests which seem most valuable for the specific examination involved, or those which he is best fitted by training or temperament to manipulate.

Because the differentiation between the "functional" and "organic" components of a case is often of paramount legal importance, all professions must ally themselves in the concerted search for methods of description which will avoid the unhappy legal contests where public opinion, subject to emotional prejudice, decides the contest.

C POSTTRAUMATIC MENTAL DETERIORATION (Dementia)

(1) *Symptomatology* The deterioration following severe head trauma is usually manifested soon after the accident, with or without a protracted delirium, obvious skull fracture, bloody spinal fluid or increased intracranial pressure. Some apparently mild head injuries are followed by gradually developing dementia. The signs and symptoms are much like those described earlier under posttraumatic personality disorders, but here the signs of dementia are gross and less debatable.

(a) *Psychological and social symptoms* The generalized retardation in initiating all activity and slowed reaction time are more obvious. Attention, "especially of the habitual and passive type," is reduced along with extensity,²⁷ vigilance, tenacity.²⁸ The memory, especially of recent events is markedly impaired, defective confabulations and pseudo-recollections, often of an absurd variety, occur. If placed under strain the memory

²⁷ Extern, "Intelligence or breadth"

defect augments the picture of disorganization, with resulting confusion and amnesia. If pushed too hard the panic state or "catastrophic reaction" occurs.^{20a} Associations are more limited in number and quality, and the likelihood of creating spontaneous combinatory forms in tests is greatly reduced.^{20a 24a, 47, 51} Complex pictures are no longer easily understood when presented for recall and analysis.^{6, 20a, 22, 24a, 47} There is definite "inability to shift" easily from one topic to another.^{24a}

Because the predominating emotion in the "organic" patient is one of apprehension and dread when under pressure, the choice of alternatives of action is often poor, hence we say the judgment is poor especially where the defective memory and other deficits blunt long-range goals or ideals. This is of great importance in the spheres of moral behavior for these aberrations are of legal concern. While he does not truly lose his ethical appreciation in general, he does suffer from a lowered ceiling of comprehension, and a constriction of his appreciation of social values. Although the patient's habits and traits of character resemble his pre-traumatic personality, it can be demonstrated that his deficits—impaired memory, relative decrease in comprehension of abstractions including ethical concepts and ideals, variable "insight for complicated relations," heightened egocentricity due to loss of awareness of larger social frames of reference—all contribute to serious incapacity for exercising proper judgment and control.

The loss of social orientation can be seen in their talking when they should not, missing or disregarding the usual social cues, and failing to show proper respect or restraint. Occasionally this mild disorientation is further complicated by senseless delusions, clumsy actions induced by fear, or even pronounced confusion and panic.

(b) Physiological impairment. More fundamental physiological impairments may cripple the patient beyond anything we have known to date, thereby altering our attitudes and expectations. Halstead²⁴ has found "that patients with frontal lobe lesions, for example, have a constricted dynamic visual field as compared with their perimetric field. The dynamic visual field is defined as the portion of the retinal field in which a visual impression can be evoked at the same instant that a form discrimination is being made by the fovea."²⁵ This means that in certain types of situations, events or objects in the peripheral portions of the visual field do not constitute a normal perceptual background, but become sporadically introduced due to the accidents of eye movements or gross shifts in posture. Variability and instability and an interesting kind of anxiety are the consequences of this alteration. The patient with a frontal lobe lesion has a full perimetric visual field, but in many types of situations he actually has available less visual field than the patient with a frank hemianopia.²⁹ Such a basic disturbance is of

²⁵ The fovea is the small depressed area near the center of the retina at which keenest daylight vision is possible.

²⁹ Hemianopia is blindness in one half of the visual field, it may affect one or both eyes.

utmost importance in determining visual efficiency and all that depends upon it; dynamic interpretation of symptom-constellations and more specific systematic rehabilitation are considerably advanced by such discoveries

(c) Course and development of symptoms A vital subject of immediate practical importance should be reviewed at this point The disappearance of these various abilities is not uniform in magnitude or time It seems that older, well established action patterns in the ethical, language, occupational and social spheres, in fact, the dominant personality patterns are the most persistent and the last to break down These are overlaid with either newly created compensatory mechanisms or exaggerated forms of old ones, or old ones, augmented This usually leads to the acceptance of the injured man as competent, although he is really balancing himself along a precarious path These older patterns provide the patient with a stable reality axis for himself In these senses the patterns are to be considered assets They are also liabilities because they are socially disarming, tending to obscure the underlying pathology in the patient, thus leading the social group to expect too much and the patient himself to aspire too high

Special mention must be made of the legal complications inherent in the dementias found in elderly people who were senile or arteriosclerotic before the injury As mentioned earlier, psychosis is much more common in the advanced age groups, furthermore, the patient's confusion due to the underlying disease may have been the source of the accident, as in cases of epilepsy (convulsive states), alcoholism or diabetes Since the deterioration of the arteriosclerotic is also organic, much more research is necessary to differentiate with even approximate certainty the damage sustained by the injury

Case of Be Ho This 24-year-old white male university student fell off a moving train on November 6, 1941 and sustained a severe right frontal concussion with probable damage to that frontal and prefrontal lobe He was unconscious for four days A spastic paralysis of the extremities on the left side was present but disappeared after five or six days He was in a typical delirium with confusion and disorientation for six days after he regained consciousness There was a complete retrograde amnesia lasting 15 months, for events leading up to the accident Early in his convalescence character changes became apparent which contrasted markedly with his behavior before the accident He had been, according to friends and relatives, a healthy, cheerful, somewhat willful youth who had no disciplinary or scholastic problems in school He was athletically skillful in several sports and was able to make the school teams One physician characterized him as being "aggressive, ambitious, outgoing and happy-go-lucky" He seemed well balanced with no undue religiosity, euphoria, depression, anxiety, neurotic defenses or psychosomatic complaints His left hemiparesis cleared up completely within three months but his mental status did not keep pace with his physical status Two months after the accident he was parrulous and partially disoriented for time and place and for persons he saw daily for weeks In answer to direct questions he confabulated various answers which were mutually contradictory He could not accept the evidence from the facts that his recent memory, particularly, and his remote memory to a less marked degree, were quite defective He insisted that he was absolutely well and should be allowed to go to a military school for pilots

If examinations of the sensorium were too pointed he attempted to get the doctor to reassure him that he was well. Tension and anxiety were obvious in his dealings with people but he was able to spend many hours peaceably in his room alone. His mood was euphoric. He claimed that he was very happy, that the accident did him some good since he had become pious, whereas before he was sinful. "Now I definitely feel superior, and am superior to what I was before the accident. I thank God for the new thoughts I now have." As time went on his religious activities grew. He read prayers daily, went to church as often as possible, called on the chaplain frequently, and talked about religion in a grandiose incoherent fashion with anyone who would listen. He wrote bad poems and indulged in artificial, stilted mannerisms of speech with exaggerated politeness and affectation. Four months after the accident he had no neurological signs on the left except for a slight muscular atrophy, hyperactive deep reflexes and a positive Babinski sign. The visual fields and fundi were normal except for slight dilatation of the retinal veins. He was now well oriented with improved recent and remote memory but the amnesia for the accident persisted. He passed the Stanford-Binet test with a score of 122 with notable improvement in retention, reversing six digits, making word pairs, arithmetic, and reversing the hands of the clock. His ability to interpret fables and proverbs, and define differences between abstract words was not as good as the other performances. His insight into his own condition and his judgment regarding his abilities remained defective, he continued to make preposterous plans for himself. A spinal fluid examination five months after the accident was essentially normal. Fifteen months after the injury he was somewhat embittered and nagged persistently because he was not permitted to attend the aviation school. He has held an electrician's job in a defense industry with only mediocre success, and with little promise of greater improvement.

SUMMARY, SECTION I

POSTTRAUMATIC PERSONALITY DISORDER

The posttraumatic personality disorders are a large group of psychoses whose classification and differentiation have been the object of voluminous publication. The standard authors cited have clarified much confusion in this complex field but oversimplification is to be avoided in order to do justice to the facts. Psychiatric and special psychological tests with improved case work will help the courts in their efforts to define the nature of the injury, its causal relation to the posttraumatic state, and the amount of disability incurred from the injury. Every competent medical witness now works up his case in accordance with the standard practices in modern textbooks of neurology and psychiatry, with roentgenograms, visual fields and fundi examinations, cerebrospinal fluid studies, encephalograms, etc. In the future he may find it profitable to demonstrate the presence of cortical damage by psychological means, especially when the physical signs alone give but incomplete testimony to the true extent of the damage.

II EXAMINATION METHODS

The need for improved methods of detecting, describing and treating disturbed mental functions is unquestionable. In patients who show little or no mental defect in an ordinary clinical examination, an extensive detailed

utmost importance in determining visual efficiency and all that depends upon it, dynamic interpretation of symptom-constellations and more specific systematic rehabilitation are considerably advanced by such discoveries

(c) Course and development of symptoms A vital subject of immediate practical importance should be reviewed at this point The disappearance of these various abilities is *not uniform in magnitude or time* It seems that older, well established action patterns in the ethical, language, occupational and social spheres, in fact, the dominant personality patterns are the most persistent and the last to break down These are overlaid with either newly created compensatory mechanisms or exaggerated forms of old ones, or old ones, augmented This usually leads to the acceptance of the injured man as competent, although he is really balancing himself along a precarious path These older patterns provide the patient with a stable reality axis for himself In these senses the patterns are to be considered assets They are also liabilities because they are socially disarming, tending to obscure the underlying pathology in the patient, thus leading the social group to expect too much and the patient himself to aspire too high

Special mention must be made of the legal complications inherent in the dementias found in elderly people who were senile or arteriosclerotic before the injury As mentioned earlier, psychosis is much more common in the advanced age groups, furthermore, the patient's confusion due to the underlying disease may have been the source of the accident, as in cases of epilepsy (convulsive states), alcoholism or diabetes Since the deterioration of the arteriosclerotic is also organic, much more research is necessary to differentiate with even approximate certainty the damage sustained by the injury

Case of Be Ho This 24-year-old white male university student fell off a moving train on November 6, 1941 and sustained a severe right frontal concussion with probable damage to that frontal and prefrontal lobe He was unconscious for four days A spastic paralysis of the extremities on the left side was present but disappeared after five or six days He was in a typical delirium with confusion and disorientation for six days after he regained consciousness There was a complete retrograde amnesia lasting 15 months, for events leading up to the accident Early in his convalescence character changes became apparent which contrasted markedly with his behavior before the accident He had been, according to friends and relatives, a healthy, cheerful, somewhat willful youth who had no disciplinary or scholastic problems in school He was athletically skillful in several sports and was able to make the school teams One physician characterized him as being "aggressive, ambitious, outgoing and happy-go-lucky" He seemed well balanced with no undue religiosity, euphoria, depression, anxiety, neurotic defenses or psychosomatic complaints His left hemiparesis cleared up completely within three months but his mental status did not keep pace with his physical status Two months after the accident he was garrulous and partially disoriented for time and place and for persons he saw daily for weeks In answer to direct questions he confabulated various answers which were mutually contradictory He could not accept the evidence from these facts that his recent memory particularly, and his remote memory to a less marked degree, were quite defective He insisted that he was absolutely well and should be allowed to go to a flying school for pilots

If examinations of the sensorium were too pointed he attempted to get the doctor to reassure him that he was well. Tension and anxiety were obvious in his dealings with people but he was able to spend many hours peaceably in his room alone. His mood was euphoric. He claimed that he was very happy, that the accident did him some good since he had become pious, whereas before he was sinful. "Now I definitely feel superior, and am superior to what I was before the accident. I thank God for the new thoughts I now have." As time went on his religious activities grew. He read prayers daily, went to church as often as possible, called on the chaplain frequently and talked about religion in a grandiose incoherent fashion with anyone who would listen. He wrote bad poems and indulged in artificial, stilted mannerisms of speech with exaggerated politeness and affectation. Four months after the accident he had no neurological signs on the left except for a slight muscular atrophy, hyperactive deep reflexes and a positive Babinski sign. The visual fields and fundi were normal except for slight dilatation of the retinal veins. He was now well oriented with improved recent and remote memory but the amnesia for the accident persisted. He passed the Stanford-Binet test with a score of 122 with notable improvement in retention, reversing six digits, making word pairs, arithmetic, and reversing the hands of the clock. His ability to interpret fables and proverbs, and define differences between abstract words was not as good as the other performances. His insight into his own condition and his judgment regarding his abilities remained defective, he continued to make preposterous plans for himself. A spinal fluid examination five months after the accident was essentially normal. Fifteen months after the injury he was somewhat embittered and nagged persistently because he was not permitted to attend the aviation school. He has held an electrician's job in a defense industry with only mediocre success, and with little promise of greater improvement.

SUMMARY, SECTION I

POSTTRAUMATIC PERSONALITY DISORDER

The posttraumatic personality disorders are a large group of psychoses whose classification and differentiation have been the object of voluminous publication. The standard authors cited have clarified much confusion in this complex field but oversimplification is to be avoided in order to do justice to the facts. Psychiatric and special psychological tests with improved case work will help the courts in their efforts to define the nature of the injury, its causal relation to the posttraumatic state, and the amount of disability incurred from the injury. Every competent medical witness now works up his case in accordance with the standard practices in modern textbooks of neurology and psychiatry, with roentgenograms, visual fields and fundi examinations, cerebrospinal fluid studies, encephalograms etc. In the future he may find it profitable to demonstrate the presence of cortical damage by psychological means, especially when the physical signs alone give but incomplete testimony to the true extent of the damage.

II EXAMINATION METHODS

The need for improved methods of detecting, describing and treating disturbed mental functions is unquestionable. In patients who show little or no mental defect in an ordinary clinical examination, an extensive detailed

psychiatric examination may reveal much gross pathology, and the use of *specific tests for evaluating specific functions* is even more likely to bring light the real damage present. Ebaugh and Benjamin,¹⁸ Strauss and Savsky,⁶⁶ Halstead,²⁴⁶ Bowman and Blau,⁸ Gross and Ehrlich²² all recommend the use of special psychological tests to bring out the defects, many of which remain operative *long after the physical symptoms have abated*.¹¹ Obvious litigants will be much interested in the results of such tests as aids in clarifying their position. The basic approaches will be described first, to be followed by exposition of the individual tests which may be of use in forensic medicine. Since many of the methods are new and abstract they will need much adequate exposition in order to be as convincing to a jury as a physical finding, but persistent usage will overcome the resistance to the new and strange.

To develop such methods a variety of approaches is being utilized. Among these diverse approaches "war injury" cases, including gunshot injuries^{40, 42, 55} and "tumor" cases^{1, 2, 8a, 8b, 90, 17a, 21, 24a, 26, 31, 43, 45, 69} have been more promising than earlier clinical descriptions of developmental anomalies, vascular cases, or cases following infections or degenerative disease.²⁴⁶ The studies of Goldstein deserve special mention for persistent utilization of qualitative methods and for thus helping open the new roads to understanding mental function. The clinical cases of Brickner, Ryland, Alford, Ackerley and Halstead are well known recent contributions. Halstead has enjoyed the advantage of having human cases who are, in effect, special preparations. The surgeons, Drs P Bailey, Paul Bucy and E A Walker were careful in doing routine operations to chart as accurately as possible the location of the lesion during operation; furthermore, clips (essential to stop hemorrhage) were inserted at strategic points to outline the lesion for roentgen examination later. Thus a revolutionary refinement was introduced making possible studies in human cases comparable to those on animals and giving access to accurate information not obtainable in any other way.

A CONTRIBUTIONS OF ANIMAL STUDIES TO METHODOLOGY

The "animal approach" would not seem at first glance to be very useful for the elucidation of human thinking, yet the work of H. H. Kluver is so outstanding in this regard that his highly original practical technique in setting up method of "equivalent stimuli," worked out with exceeding interpretation with his superb analysis of the theoretical questions involved in the meaningful experiment and of the difficulties of correct interpretation of results, make this work necessary reading. Traditional methods of examination of cerebral function have been inadequate to correlate specific functions and Kluver. The latter author utilizing monkeys, memory parietal lobe, investigators brain lesions which could be studied more profitably. He is a school for reasoning defined lesions available in humans until quite recently. He is a school for reasoning notably Carlyle Jacobsen²⁰ working with apes, also. It is because the studies on animals are useful for understanding man beings.

that this work is presented "It has not yet been generally recognized, unfortunately, that the considerations which Kluver has raised concerning methods of studying behavior apply to *any analysis of behavior* whether the organism involved be insect or rat, monkey or man" ^{24a} Lashley justly praised this method in 1933 when he wrote that

"Dr Kluver's monograph sets a new standard for analytic studies of behavior. He has proposed the question, Just what properties in complex sensory situations are significant for the animal's reactions? and has carried out the investigation with unique thoroughness. As a result, he presents for the first time something approaching a complete picture of the perceptual world of an animal. This perceptual organization is surprisingly like that of man. Not only are the animals sensitive to the same physical stimuli but for them also the relational properties of the situations are the same. As with man, reactions are but little dependent upon the simple physical properties of the stimulus but rather upon abstract relations which may subsist in physically unlike situations. The processes of abstraction and generalization involved in the perception of similarity and difference seem as efficient in the Macaques as in man and not fundamentally different

* * * * *

"The most immediate value of the study is in laying a foundation for investigations of the neurophysiology of behavior. Clinical evidence is far from adequate to settle the major problems of nervous integration and of the organic mental disorders and must be supplemented by experimental studies. But experimental neurology has made little progress toward an understanding of the mechanisms of thinking for lack of an adequate knowledge of the normal behavior of the animals studied and of means of detecting any but the grossest disorders of behavior. The data and methods, here made available, open the way for an experimental attack upon many of the problems of sensory agnosia and the organic disturbances of thinking.

"In brief space it is impossible even to mention many other problems of psychology upon which the data accumulated by Dr Kluver have significant bearing. In his own interpretation of the material he has maintained a wise conservatism. His discussion of the principles of interpretation in psychological studies seems to me one of the most important recent contributions to theoretical psychology. He is skeptical of formulas, whether they be the schemata of behaviorism, the field properties of the configurationists, or the images and ideas of structuralism, and justifies an experimental and phenomenological approach to the problems. In the infancy of a science generalizations are rarely true beyond narrow and too often undefined limits. The important contributions to psychology are not the classifications which confuse the issues, the explanations which overload the problems, and the neologisms which disguise our ignorance but the tracing of relations through the intricate web of dependent processes which is mind. Always the question, How? punctures the bubble of theory, and the answer is to be sought in analysis and ever more analysis" ^{24b}

B METHOD OF EQUIVALENT STIMULI

The need for investigating behavior by this method is well described by Halstead

The problem of equivalence in the analysis of behavior has been dealt with in its various aspects by Kluver and will be considered here only in a general way. This problem arises most prominently in connection with various forms of behavior which remain unaltered in the presence of marked change in the environmental stimulus con-

stellation Such forms of behavior do not persist unaltered in the presence of all changes in the stimulus constellation, however Using Kluver's terminology, it becomes convenient to refer to the stimuli in the first situation as "equivalent stimuli" and to those in the second (in which the response in question is altered) as "non-equivalent stimuli" Interest in such differentially stable forms of behavior does not end with the discovery (for a particular response) of a number of "equivalent" stimuli, i e, an "equivalence range" In fact, primary concern in a given situation is an answer to the question "What property or characteristic of equivalent stimuli is responsible for equivalence?" It may be observed, for example, that under certain conditions (a) solid squares, solid and outline ellipses, solid and outline circles and line drawings of a "star" of certain sizes, when projected symmetrically at the monocular fixation point of a nulle vision hemianopic patient, will be seen by him as whole or "completed" figures whereas (b) squares or ellipses of a particular size, straight lines, diagonal lines, less than half a circle, or a picture of a dog, face, bottle or butterfly will be seen as part figures or "uncompleted" In line with the preceding discussion, the stimuli of A, in terms of "completion" behavior, may be referred to as "equivalent stimuli" whereas the stimuli of B with reference to "completion" behavior may be termed "non-equivalent stimuli" Clearly, where questions of such biological importance as "seeing" and "not seeing" are involved, it is not sufficient to know that A stimuli and B stimuli exist It becomes important to know what property or characteristic of the A stimuli makes it possible for them to be "seen," i e, "completed" It should be clearly recognized that whatever this property or characteristic is, it is, in a certain sense, present in the A stimuli only and yet cannot be defined without analyzing the properties of the B stimuli

The "method of equivalent stimuli" is utilized in novel form by Halstead^{24a} in his human cases which have been carefully studied for a long period, some of them for five or more years. His observations are not dependent upon sporadic clinical investigation but are a part of a systematic research program in the best sense He finds that the grouping behavior of individuals with one frontal lobe, whether right or left, differed from normals in the following ways reduction of the number of objects "spontaneously" employed, reduction in recall of objects from the test-field; absence of grouping effect in recall performance, differences in the distribution of the groups produced Interested readers are referred to his original paper for a presentation of his test materials and methods because all qualitative examination technics required unusual care and training Unfortunately some of these methods, especially the Rorschach ink-blot experiment, have acquired unwarranted criticism because of superficial application by untrained workers

C PREFRONTAL LOBOTOMY APPROACH

Recently a unique opportunity for studying cerebral function has been opened up by the "prefrontal lobotomy"³⁰ cases,^{17a, 17b} i e, psychotics treated by the Moniz or other methods of prefrontal lobotomy for relief of psychiatric symptoms This would seem to be an ideal and plentiful source of

³⁰ Prefrontal lobotomy is the surgical operation in which the prefrontal lobes of the brain are separated mechanically from the frontal lobes

desirable material but there are several disadvantages. The subjects were not "normal" before surgery and may introduce too many uncontrollable variables in all evaluations, moreover, the proponents of these methods have not employed the more refined systematic methods over a sufficiently long period of time to yield new results.

D STANDARDIZED MENTAL AND PERSONALITY TESTS

(1) *Actual Life Performance* In order to gain a better perspective of the range of mental testing methods it might clarify the profusion of available tests to categorize them as tests of (1) actual life performance, (2) general abilities (abstraction), or (3) special functions (memory, attention retardation). Bleuler⁹ said aptly, "all theoretical tests can be passed faultlessly, while the patient is perfectly unfit to manage his own affairs—Life is really the only sure touchstone. What is here said concerning theoretic examinations should only be considered as illustrations and suggestions for individual procedures. It is impossible to prescribe all that is to be examined in the individual case. It is not always of special importance what one talks with the patients, but how one observes and how one concludes—The most important thing is always the judgment of the observations and inquiries. Despite all rules the intelligence test is as much a test of the doctor's intelligence as of the patient's intelligence." Students will have no trouble in recognizing the adherence of K. Goldstein, H. Kluver and W. C. Halstead to these principles. Owing to a number of limitations which are discussed by K. Goldstein,^{20a} it has not been found feasible to obtain the apparently ideal description of a patient's mental status from his behavior in his accustomed environment. In the test situation the patient was not actually working at his old job. First, the more the project resembled the real job, the more likely it was to introduce emotional factors based upon the man's willingness to recover with or without compensation. Secondly, the operations involved in most skilled occupations are too complex to be adequately controlled against the performances of similar patients or of normal individuals. Thirdly, the simulated work does not reveal the defects in the spheres of general abilities, but only in the specific kind of work being done. Goldstein believes that general tests reveal much more about the causes for the failure in the specific operations. However, if these three limitations are kept in mind, testing a patient under simulated real-life conditions has advantages which may help juries to make decisions. Work shops are also of great therapeutic aid to convalescent patients as an extension of the usual hospital occupational therapy, for patients are more strongly motivated to do their best, and may re-acquire lost skills.

E TESTS FOR ABSTRACT ABILITY

Although Kluver makes abundantly clear that the concepts of "abstract" and "concrete" are relative terms, definable only with a special experimental

situation, the tests for abstract ability are among the most important we have for the following reasons given by Goldstein ^{20a} (1) The experimental frame of reference can be controlled (2) The results can be recorded in detail with reasonable accuracy, making possible comparative data and statistical analysis Graphic representation is possible and often useful (3) All types of patients can usually be motivated, if managed with skill, to cooperate in working at appropriately selected tests (4) Even sick patients can be given tests repeatedly under similarly controlled conditions because of their simplicity (5) Previous training and attitudes are minimized and hence large groups can be compared, whereas in real life testing of special abilities such comparisons are difficult It is important to realize that no one test can encompass the whole field of abstract thinking Moreover, it is even more important not to judge the patient's performance merely by end results but by his mode of achieving them Simple plus and minus results are inadequate for final evaluation of capacities It is necessary to understand *how* the patient achieves his results, the methods or devices by which he attains them regardless of whether they are right or wrong K Goldstein has presented many excellent examples of such analysis ^{6 and 20a} The specific experiment used is chosen for what it will elicit but the evaluation of the results is not mechanical as in standardized tests such as the Binet, Terman or Bellevue-Wechsler

Many tests have been devised for qualitative analysis utilizing heterogeneous material ^{24a} The best use of these has been in Halstead's special adaptation, designated as a "category test" ^{24a} Here the performance of patients with single frontal lobe lesions exhibits definite properties which can be graphically presented and compared with those of normal individuals and of patients with lesions of other types

For testing abstract thinking, the usual mental status examinations in the psychiatric texts have a variable range of materials such as numbers, stories, proverbs, and problems The addition of pictures and diagrams in test situations is helpful A short compact test utilizing these principles was devised for rapid clinical use by Dr J D Benjamin and associates at the Colorado Psychopathic Hospital Many doctors use the readily available Wells and Ruesch "Mental Examiners Handbook" ⁷¹ as a source of diverse test material employing verbal and pictorial problems

The Shipley-Hartford test is a standardized vocabulary and abstract thinking test which offers a helpfully quick (20 minutes) but not very complete means of estimating whether gross organic defect is present ⁶¹ Methods like this one may find favor in cases in which the defects are quite extensive

Benton and Howell ⁵ have published a case study illustrating the use of several tests mentioned (Shipley, Rorschach) and in addition the Kohs Block Test, ³⁶ the Bolles Object Sorting Test, ⁷ the latter superficially similar but differing from Halstead's category test, the Weigle Color-Form Sorting Test, ³ and the similarities test of the Bellevue scale ⁷¹

D Wechsler⁷¹ offers the Bellevue-Wechsler test as a means of detecting gross organic damage. He lists the following results (subject to many qualifications) as indicative of an organic mental status: (1) Verbal scores higher than performance test scores (2) Information relatively good (3) Comprehension relatively good (4) Arithmetic poor (5) Similarities poor (6) Memory span very poor, particularly for digits backwards (7) Block design very poor (8) Object assembly poor (9) Digit symbol very poor (10) Small variability when verbal and performance test scores are considered separately.

Further information regarding methods of testing deterioration may be studied in the clinical fields other than the organic psychoses. The expert work of E. Hanfman using the Vigotsky test,²⁹ Henry Murray's popular "Thematic Apperception" test⁴⁴ and H. Babcock's^{4a, 4b} studies on deterioration are interesting in this regard.

One serious drawback to all these tests is the absence of a test record taken before the injury occurred. Relatively few people in civilian life have ever had even a standard intelligence test. In all tests inferences from the contemporary record regarding the pretraumatic status furnishes the basis for describing the changes said to be due to trauma. More often the evidence for deterioration is compared with the pretraumatic clinical picture as obtained by history from witnesses (friends, relatives and business associates). It would be highly desirable to have available pretraumatic behavior records taken in the same medium as records made posttraumatically. One such medium is available for most patients—their handwriting. Handwriting analysis has demonstrated its clinical usefulness in the competent hands of Klages, Pulver and their pupils in personality interpretation.^{32a, 32b, 33} Their studies have not included large groups of the posttraumatic psychoses although there are some suggestions that this would be a useful field of inquiry. The old psychiatric texts (Bleuler) contain samples of handwriting allegedly recognizable as "organic."

One of the best developed qualitative methods of examination is the so-called Rorschach Ink-Blot experiment³⁴. In the hands of skillful students the deductions possible from the patient's replies to these ten standardized ink-blot tests are often startlingly true. E. Oberholzer⁴⁴ published an excellent paper on the case of posttraumatic personality which has been a model for later work. Incidentally Oberholzer while in Switzerland was permitted to use his material as legally admissible evidence in his capacity as witness in head injury cases. Piotrowski⁵¹ lists the following "findings" as characteristic of an "organic's" Rorschach performance: 1 Reduction in number of responses 2 Absence of kinesthetic responses³¹ 3 Form per cent lowered 4 Prolonged time needed for reply 5 Color naming 6 Repetition 7 Perseveration 8 Impotence (giving a response in spite of the recognition of its inadequacy) 9 Perplexity 10 Automatic phrases. The presence

³¹ Kinesthetic responses are those which contain human figures seen in significant action.

of five or more of these "signs" is supposed to indicate the presence of head injury, according to Piotrowski, but other work questions the reliability of such atomistic dissection²⁹ The real value of Rorschach interpretation derives not from single signs which it yields, but from its capacity for revealing action patterns or levels of performance

Kelley has summarized the Rorschach articles available up to 1942 that relate to organic cases²⁹ Rorschach technic, like any other technical skill is not acquired without genuine application, intelligent direction and careful study of many types of clinical cases Its use of field concepts³² is an excellent introduction to the methods of qualitative analysis The interpretations made possible by this method are a convincing demonstration of the value of the general approach when compared with the more atomistic approaches, for here an evaluation of many other qualities of the personality are possible besides the "intelligence" Some of these qualities are capacity for inward living, capacity for external expression, affective adaptability, oppositionality, creativeness and originality, stereotypy, capacity for dealing with ideas and things, accuracy of perception, etc There is the opportunity in most records of describing the type of neurosis concomitant with the head injury and of estimating the availability for therapy It may be remarked in passing that, in general, neuroses are not improved by cortical damage, including lobotomy

F TESTS OF SPECIAL ABILITIES

Tests of special abilities are numerous and helpful The addition test of Kraepelin remains one of the best for studying the patient's attention, capacity to learn, persistence and fatigability^{20a, 63} Performance graphs are of real help in visualizing the experiment The slope at the beginning, the fluctuations of the plateau, the gradual decline or sudden end, the general average height, the number of errors are studied for the light they throw on the nature of the patient's abilities The reaction test combined with a situation-compelling choice is favored by K Goldstein^{20a} He also uses ergographic tests developed in general physiology for studying fatigue and work capacity The special tests in psychometric examinations for recall, calculation, various memory tests both visual and auditory, dexterity tests for various types of performance all furnish material for exploring the patient's abilities

G PSYCHOANALYTIC STUDIES OF TRAUMATIC PSYCHOSES

The content of traumatic psychoses has not been extensively examined by psychoanalysts yet the few papers on other "organics" available furnish interesting leads for further work^{15a, 15b, 16, 30, 36b, 50} Fenichel states in sum-

³² A field concept describes the "subject-object" (patient-environment) relationship as an active, organized, continuous process

mary "Ferenczi and Hollos seem to have proved that much of the symptomatology of general paralysis is not a direct consequence of the degenerative processes of the brain, but an indirect pathoneurotic reaction to the patient's own observation of his organically determined loss of cerebral function. Psychoses which develop after mutilating accidents are also based on a narcissistic regression³³ of the pathoneurotic type. The function of these psychoses is very evidently to deny the unpleasant reality, and their clinical picture is dominated by the conflict between the tendency to deny and the perception of the real state of affairs so that projections, etc. appear."³⁴ Kardiner's large monograph on "Traumatic Neuroses"³⁵ has many interesting case histories with emphasis upon the social frame of reference, developmental and conditioning forces, which are not our immediate interest. His emphasis upon the "adaptation" principle,³⁶ and comparative neglect of the instinctual forces³⁷ will be received with varying judgments, depending upon one's point of view. Most psychoanalysts will feel the deficiency serious, whereas non-analytic readers may find this simplification attractive.

Among the special tests, some readers will miss the voluminous work on problems in aphasia, apraxia,³⁸ agnosia,³⁷ amusia.³⁸ These and other "individual" defects are properly examined as a part of a standard careful neurological examination. The theoretical and therapeutic problems involved are discussed in the publications already cited.

SUMMARY

The three types of traumatic psychoses have been discussed with special emphasis upon those cases in which the physical indicators are inadequate to measure the damage. Even such gross disturbance as a visual agnosia may soon be compensated for to a remarkable degree even though it persists, incapacitating functions such as the "constricted dynamic field" are being newly uncovered which further stress the need for a careful examination for all patients to establish their true physiological competence. In the majority of cases psychological means are necessary for evaluating the extensity and severity of the damage to a person's capacities and personality organization.

³³ Narcissistic regression refers to increased evaluation of the self, causing greater preoccupation with the body and its functions, hypochondriasis or undue concern over the body, greater selfishness, egocentricity, and sensitivity to acts which may disturb the patient.

³⁴ Kardiner believes that although elementary drives (instincts) exist, the symptoms we observe are not to be construed as direct evidence of the operation of these drives. He describes the neuroses as action syndromes whose form is more important than the content. The adaptations, made by various functioning units of the whole personality in its effort to gain effectual stabilization, are his major consideration.

³⁵ Instincts are elementary drives such as eating, eliminating, mating and self-preservation.

³⁶ Apraxia is the loss of ability to perform purposeful movements.

³⁷ Agnosia is the inability to recognize the meaning of sensory stimuli although the organs mediating them are organically intact.

³⁸ Amusia is the inability to produce or to comprehend musical sounds.

Several problems, important in legal actions, are discussed (1) The differentiation between organic and neurotic behavior patterns (2) Amnesia legal responsibility and dynamics of the "organic" syndrome and deterioration (3) Methods of distinguishing the true organic defects, even though obscured by compensatory mechanisms which give the superficial appearance of a good adjustment Such differentiations are not always easy even though legally important Much more groundwork needs to be done and the head-injury cases from the war will provide added impetus for study and treatment Scientifically, these cases together with the "tumor" and "lobotomy" series offer an unparalleled opportunity for man to study cerebral function by methods unavailable up to this time Although methods of study have merit, it is believed that the "qualitative" technique promise the most fruitful results

BIBLIOGRAPHY

- 1 ACKERLY, S Instinctive emotional and mental changes following prefrontal lobectomy, *Am Jr Psychiat*, 1935, xcii, 717-728
- 2 ALFORD, L B Defects of intelligence from focal lesions within the central part of left cerebral hemisphere, *Am Jr Psychiat*, 1937, xciv, 615-633
- 3 ALLEN, A M, MOORE, M, and DALY, B B Subdural hemorrhage in patients with mental disease a statistical study, *New England Jr Med*, 1940, ccxxxiii, 324-328
- 4a BABCOCK, H *Arch Psychol*, Monograph No 117, 1930 Also SIMMINS, C, Jr, *Psychol Sci*, 1933, lxxix, 704-734
- 4b BABCOCK, H *Dementia praecox*, 1935, New York
- 5 BENTON, A L, and HOWELL, IRA L Psychological tests following head injury in a case, *Psychosom Med*, 1941, iii, 138-151
- 6 BLEULER, E *Textbook of psychiatry*, 1924, The Macmillan Company, New York
- 7 BOLLES, M M The basis of pertinence, *Arch Psychol*, 1937, xxxxi, 51
- 8 BOWMAN, K M, and BLAU, A Psychotic states following head and brain injury in adults and children In Brock (Ed), *Injuries of the skull, brain and spinal cord*, 1940, Williams and Wilkins, Baltimore
- 9a BRICKNER, R M An interpretation of frontal lobe function based upon the study of a case of partial bilateral frontal lobectomy, *Proc Assoc Research Nerv and Ment Dis*, 1934, xiii, 259-35
- 9b IDEM Intellectual functions of the frontal lobes, 1936, The Macmillan Company, New York
- 9c IDEM Bilateral frontal lobectomy follow up report of a case, *Arch Neurol and Psychiat*, 1939, xli, 580-585
- 10 CHENEY, C O *Outlines for psychiatric examinations*, New York State Department of Mental Hygiene, 1934, State Hospital Press, Utica, New York
- 11 CONKEY, R C Psychological changes associated with head injuries, *Arch Psychol*, 1938, xxxlii, 62
- 12 CUMINGS, J N Uremia following head injury, *Jr Neurol and Psychiat*, 1942, v, 40-46
- 13 EBAUGH, F G, and BENJAMIN, J D Trauma and mental disorders In BRAHDY, L, and KAHN, S *Trauma and disease*, 1941, 2nd Edition, Lea & Febiger, Philadelphia

- 14 EICHLER, P Pseudotabetic and pseudoparalytic manifestations in concussion psychosis, *Arch f Psychiat*, 1939, cix, 282-302
- 15a FENICHEL, OTTO Outline of clinical psychoanalysis, *Psychoanal Quart*, 1932, i, 292-342
- 15b IDEM Outline of clinical psychoanalysis, 1934, The Psychoanalytic Quarterly Press and W W Norton and Co, Inc, 70 Fifth Ave, New York
- 16 FERENCZI, S, and HOLLOS Psychoneurosis and general paresis, *Nerv and Mental Dis Monograph Series*, 1925, New York
- 17a FREEMAN, W, and WATTS, J W An interpretation of the functions of the frontal lobe based upon observation in forty-eight cases of prefrontal lobotomy, *Yale Jr Biol and Med*, 1939, ii, 527-539
- Pt b IDEM Prefrontal lobotomy, *Bull New York Acad Med*, 1942, 794 to 812
- Kc IDEM Frontal lobes and consciousness of self, *Psychosom Med*, 1941, iii, 111-119
- es' FULTON, J F Physiology of the nervous system, 1938, Oxford University Press, London, pp 232-263
- H1s GOLDSTEIN, H H Traumatic psychoses, *Illinois Med Jr*, 1939, lxxvi, 242-246
- the GOLDSTEIN, KURT Brain injuries in war, 1942, Grune and Stratton, New York
- upon IDEM The significance of the frontal lobes for mental performances, *Jr Neurol and Psychopath*, 1936, xvi, 27
- serior DON, ALFRED Delayed mental disorders following cranial traumatism and their a psychopathological interpretation, *Jr Nerv and Ment Dis*, 1933, lxxix, 259
- 22 GROSS, S W, and EHRLICH, W Diagnosis and treatment of head injuries, 1940, P Hoeber Co, New York.
- 23 HALL, G W The relation of psychiatric and neurotic disturbances to head injury, *Illinois Med Jr*, 1925, xxxviii, pp 279-286 See Strauss and Savitsky loc cit
- 24a HALSTEAD, W C Preliminary analysis of grouping behavior in patients with cerebral injury by the method of equivalent and non equivalent stimuli, *Am Jr Psychiat*, 1940, xcvi, 1263-1294
- 24b IDEM Personal Communication (Case 1 of Series cited above)
- 24c IDEM The effects of cerebellar lesions upon the habituation of postrotational nystagmus, *Comp Psychol, Monogr*, 1935, xii, 130
- 24d IDEM A note on the Bartley effect in the estimation of equivalent brightness Reprinted from the *Jr Exper Psychol*, 1941, xxi, 524-528
- 24e IDEM Experimental analysis of the effects of localized cerebral injury in man, *Jr Am Med Assoc.*, 1937, cviii, 1624
- 24f IDEM A method for the quantitative recording of eye movements, *Jr Psychol*, 1938, vi, 177-180
- 24g HALSTAD, WARD C, WALKER, A EARL, and BUTY, PAUL C Sparing and nonsparing of "macular" vision associated with occipital lobectomy in man Reprinted from the *Arch Ophth*, 1940, lxi, 948-962
- St h HALSTEAD, W C Behavioral effects of lesions of the frontal lobe in man, *Arch Neurol and Psychiat*, 1939, xli, 780-783
- of, HALSTEAD, W C Paper read before Chicago Neurological Society Oct, 1942 To be published
- 25 HANFMAN, E, and KASANIN, J Conceptual thinking in schizophrenia, *Nervous and Mental Disease Monographs*, 1942, No 67, New York
- 26 HEBB, D O, and PENFIELD, W Human behavior after extensive bilateral removal from the frontal lobes, *Arch Neurol and Psychiat*, 1940, xli, 421-438
- 27 HENDERSON, D K, and GILLESPIE, R D A textbook of psychiatry, 3rd Edition, 1932, Oxford University Press, London
- 28 HOCH, P, and DAVIDOFF, E Traumatic psychoses, *Jr Nerv and Ment Dis*, 1939, xc, 337-343

- 29 JACOBSEN, C F, and NISSEN, H W Studies in cerebral function in primates IV The effects of frontal lobe lesions on the delayed alternation habit in monkeys, Jr Comp Psychol, 1937, xxiii, 101
- 30 JELLIFFE, S E, and WHITE, W A Disease of the nervous system, 6th Ed, 1935, Lea and Febiger, Philadelphia
- 31 KAHN, E, and THOMPSON, L J Concerning Pick's disease, Am Jr Psychiat, 1934, xii, 937-946
- 32a KLAGES, LUDWIG Handschrift und Charakter, 1932, Barth, Leipzig
- 32b IDEM Grundlegung der Wissenschaft vom Ausdruck, 1936, Barth, Leipzig
- 33a KARDINER, A . Bio-analysis of epileptic reaction, Psychoanalyt Quart, 1932, i, 375
- 33b IDEM The traumatic neuroses of war, 1941, National Research Council, Washington, D C
- 33c KENNEDY, FOSTER Head injuries effects and their appraisal, Arch Neurol and Psychiat, 1932, xxvii, 811
- 34 KLOPPER, B, and KELLEY, D The Rorschach Technique, 1942, World Book Co, Yonkers, New York. (Excellent Bibliography)
- 35 KOHS, S C Intelligence measurement, 1923, Macmillan Co, New York
- 36a KLUVER, HEINRICH Behavior mechanisms in monkeys, 1933, The University of Chicago Press, Chicago, Ill
- 36b IDEM Visual disturbances after cerebral lesions, Psychol Bull, 1927, xxiv, 316-358
- 36c IDEM The equivalence of stimuli in the behavior of monkeys, Jr Genet Psychol, 1931, xxxix, 3-27
- 36d IDEM The study of personality and the method of equivalent and non-equivalent stimuli, Character and Personality, 1936, v, 91-112
- 37 LASHLEY, K S Brain mechanisms and intelligence, 1929, Univ of Chicago Press, Chicago
- 38 LENNOX, W G, GIBBS, E L, and GIBBS, F A Inheritance of cerebral dysrhythmia and epilepsy, Arch Neurol and Psychiat, 1940, xlv, 1155-1183
- 39 LEWINSON, T S, and ZUBIN, J Handwriting analysis, 1942, King's Crown Press (Columbia Univ)
- 40 The Medical Department of the U S Army in the World War, Volume X, Neuropsychiatry, Washington U S Government Printing Office, 1929
- 41 MEYER, A The anatomical facts and clinical varieties of traumatic insanity, Am Jr Insanity, 1904, lx, 373
- 42 MILLER, E The neuroses in war, 1940, The Macmillan Co, New York
- 43 MIXTER, W J, TILLOTSON, K J, and WIES, D Reports of partial frontal lobectomy and frontal lobotomy on three patients one chronic epileptic and two cases of chronic agitated depression, Psychosom Med, 1941, iii, 26-37
- 44 MURRAY, H A, et al Explorations in personality, 1938, Oxford University Press, New York.
- 45 NICHOLS, I C, and HUNT, J M A case of partial bilateral frontal lobectomy, Am Jr Psychiat, 1940, xcvi, 1063-1083
- 46 NOYES, A P Modern clinical psychiatry, 2nd Ed, 1940, W B Saunders Co, Philadelphia
- 47 OBERHOLZER, E Zur Differentialdiagnose psychischer Folgezustände nach Schädeltraumen mittels des Rorschachschen Formdeutversuchs, Ztschr f d ges Neurol u Psychiat, 1931, cxxxvi, 596
- 48 OLIVECRONA, H Corticomeningeal scars in traumatic epilepsy localization by pneumographic examination of the subdural space, Arch Neurol and Psychiat, 1941, xlv, 666-671
- 49 PENFIELD, W, and KEITH, H M Focal epileptogenic lesions of birth and infancy with report of eight cases, Am Jr Dis Child, 1940, lxx, 718-738

- 50 PENFIELD, W, and HUMPHREYS, S Epileptogenous lesions of the brain histologic study, Arch Neurol and Psychiat, 1940, xliii, 240-261 See also FOERSTER, O and PENFIELD, W The structural basis of traumatic epilepsy and results of radical operation, Brain, 1930, lxi, 99
- 51 PIOTROWSKY, Z A The Rorschach ink-blot method in organic disturbances of the central nervous system, Jr Nerv and Ment Dis, 1937, lxxvi, 525, 537
- 52 POWELL, ELLIS Cerebral malnutrition and its diagnosis, New Internat Clin, Series 4, 1941, i, 101-128
- 53 PULVER, MAX Symbolik der Handschrift, 1931, Füssli, Zurich and Leipzig
- 54 ROSENBAUM, M, et al Intracranial blood flow in dementia paralytica, cerebral atrophy and schizophrenia, Arch Neurol and Psychiat, 1942, xlvii, 793-799
- 55 ROTHSCHILD, DAVID Neuropathologic changes in arteriosclerotic psychoses and their psychiatric significance, Arch Neurol and Psychiat, 1942, xlviii, 417-436 Abstract in Year Book of Neurology, Psychiatry and Endocrinology, 1941, The Year Book Publishers, Chicago
- 56 RUSKEN, W Psychogenic manifestations coinciding with atrophic processes of the brain, Ztschr f d ges Neurol u Psychiat, 1940, clxx, 637-666
- 57 RYLANDER, G Personality changes after operations on the frontal lobes, 1939, Humphrey Milford, Oxford University Press, London
- 58 SCHALLER, W F Affect-effects of head injury, Jr Am Med Assoc, 1939, cxiii, 1779-1785
- 59 SCHILDER, P Psychic disturbances after head injuries, Am Jr Psychiat, 1934, xci, 155-188
- 60 SHAPIRO, L B Schizophrenic like psychoses following head injuries, Illinois Med Jr, 1939, lxxvi, 250-254
- 61 SHIPLEY, W C A self-administering scale for measuring intellectual impairment and deterioration, Jr Psychol, 1940, ix, 371-377 See also SHIPLEY, W C, and BURLINGAME, C C A convenient self-administering scale for measuring intellectual impairment in psychotics, read at American Psychiatric Association, Cincinnati, Ohio, May 20-24, 1940
- 62 STEINBERG, D L Psychotic reaction following trauma, Illinois Med Jr, 1939, lxxvi, 246-250
- 63 STERN, WILLIAM General psychology, 1938, The Macmillan Co, New York
- 64 STONE, T T, and BRAMS, W A Ultimate results in severe craniocerebral injury, Jr Am Med Assoc, 1927, lxxviii, 1056-1058
- 65 STRAUSS, A A and WERNER, H Conceptual thinking in the brain-injured child, Jr Nerv and Ment Dis, 1942, lcvii, 153-172
- 66 STRAUSS, I, and SAVITSKY, N Head injury, neurologic and psychiatric aspects, Arch Neurol and Psychiat, 1934, lxxv, 893, also Sequelae of head injury, psychogenic factor, Am Jr Psychiat, 1934, xci, 189 (An outstanding article discussing trauma in relation to other psychoses)
- 67 STRECKER, EDW, and EBAUGH, F G Clinical psychiatry, 5th Ed, 1940, Blakiston's Sons & Co, Philadelphia
- 68a THOMAS, CHARLES C Medical Progress Annual, 1942, iii, Ed by Robert N Nye, page 371
- 68b IDEM Medical Progress Annual, 1942, i, Ed by Robert N Nye
- 69 VIETS, HENRY Notes on war injuries of the frontal lobe, Albany Med Annual, Albany, 1920, xli, 14
- 70 WEBER, F P, and BLUM, K Acute pulmonary edema with hypoglycemic coma, Jr Neurol and Psychiat, 1942, i, 37-39
- 71 WECHSLER, D The measurement of adult intelligence, 1929, 2nd Edition, The Williams and Wilkins Company, Baltimore, Md

- 72 WECHSLER, I S Trauma and the nervous system, Jr Am Med Assoc, 1935, civ, 519
- 73 WEIGLE, E Zur psychologic sogennanter Abstraktionsprozesse, Ztschr f Psychol, 1929, ciii, 1, 257 Abridged English Translation by RIOCH, M J J: Abnorm and Social Psychol, 1941, xxxvi, 3
- 74 WELLS, F L, and RUESCH, J Mental examiners handbook, 1942, Psychological Corporation, New York (From Psychiatric Laboratories of the Mass General Hosp)
- 75 WELLS, F L Mental tests in clinical practice, 1927, World Book Co, New York
- 76 WELLS, F L, and KELLEY, C M Intelligence and psychosis, Am J: Psychiat, 1920, lxxvii, 16
- 77 WINKELMAN, N W, and ECKEL, D L Brain trauma, histopathology during early stages, Arch Neurol and Psychiat, 1934, xxxi, 956-986

The Department of Legal Medicine of the Harvard Medical School
Announces Its Sponsorship of

SCIENTIFIC PROOF AND RELATIONS OF LAW AND MEDICINE

A symposium series on law-science problems with particular reference to
law-medicine problems

HUBERT WINSTON SMITH, A B, M B A, L L B, M D, *Editor-in-Chief, Associate in
Medical-Legal Research, Harvard Law School and Department of Legal Medicine,
Harvard Medical School*

Note The Symposium Series is scheduled for publication in the following journals

MEDICAL JOURNALS

- 1 American Journal of Psychiatry (Am J Psychiat), 111 St. George St., Toronto, Canada, price \$1 75 a copy
- 2 *Annals of Internal Medicine* (Ann Int Med), Green and Redwood Streets, Baltimore, Maryland
- 3 *Annals of Surgery* (Ann Surg), East Washington Square, Philadelphia, Pennsylvania
- 4 *Clinics*, East Washington Square, Philadelphia, Pennsylvania, price \$2 00 a copy
- 5 *Medicine*, Johns Hopkins Hospital, Baltimore, Maryland, price \$1 50 a copy

LEGAL JOURNALS

- 1 *Boston University Law Review* (B U L Rev), 11 Ashburton Place, Boston, Massachusetts, price \$70 a copy
- 2 *California Law Review* (Calif L Rev), Boalt Hall of Law, Berkeley, California, price \$90 a copy
- 3 *Harvard Law Review* (Harv L Rev), Harvard Law School, Cambridge, Massachusetts, \$85 a copy
- 4 *Michigan Law Review* (Mich L Rev), Hutchins Hall, Ann Arbor, Mich, price \$80 a copy
- 5 *North Carolina Law Review* (N C L Rev), University of North Carolina, Chapel Hill, N C, price \$80 a copy
- 6 *Rocky Mountain Law Review* (Rocky Mt. L Rev), University of Colorado Law School, Boulder, Colorado, price \$1 00 a copy
- 7 *Southern California Law Review* (So Calif L Rev), University Park, Los Angeles, California, price \$1 00 a copy
- 8 *Tennessee Law Review* (Tenn L Rev), 720 West Maine Avenue, Knoxville, Tennessee, price \$75 a copy
- 9 *University of Chicago Law Review* (U of Chi L Rev), Chicago, Ill, price \$75 a copy
- 10 *Virginia Law Review* (Va L Rev), Clark Memorial Hall, Charlottesville, Virginia, price \$1 00 a copy
- 11 *Yale Law Journal* (Yale L J), Yale Station, New Haven, Connecticut, price \$80 a copy
- 12 *Indiana Law Journal* (Ind L J), 38 Maxwell Hall, Bloomington, Ind., price, \$75

If a journal is italicized this signifies it is devoting its entire April 1943 issue to the publication program

I PROJECTION PAPER

- (1) Smith, Hubert Winston, Scientific Proof and Relations of Law and Medicine, 18 ANN
INT MED (April 1943) 450, (April 1943) 1 CLINICS 1353 (April 1943) 23 B U L

Rev —, (April 1943) 15 Rocky Mt L Rev —, 17 So Calif L Rev (April 1943) —, 20 U of Chi L Rev (April 1943) —, 29 Va L Rev (April 1943) —, 53 Yale L J (May 1943) —

PART I

LAW-MEDICINE PROBLEMS AND SCIENTIFIC THOUGHT

II CLINICAL FORENSIC MEDICINE

- (2) Brahdý,* Dr Leopold and Kahn,** Dr Samuel, Clinical Approach to Alleged Traumatic Disease, 18 ANN INT MED (April 1943) 491, 23 B U L Rev (April 1943) —

(* Physician in Charge of Occupational Diseases and Injuries of Municipal Employees, New York City, Fellow, American College of Chest Physicians, Chairman, Committee on Tuberculosis in Industry, American Trudeau Society)

(** Medical Examiner in Division of Workmen's Compensation, New York State Department of Labor)

- (3) Moritz,* Dr Alan Richards, The Mechanisms of Head Injury, 117 Ann Surg (April 1943) 562, 23 B U L Rev (April 1943) —

(* Professor of Legal Medicine, Harvard Medical School, Lecturer in Legal Medicine, Tufts College and Boston University, Pathologist to the Department of Public Safety and Consulting Pathologist to the Department of Mental Health of the Commonwealth of Massachusetts)

- (4) Denny-Brown,* Dr Derek Ernest, Factors of Importance in Head Injury—A General Survey, 1 Clinics (April 1943) 1405, 29 Va L Rev (April 1943) —

(* F R C P, London, Professor of Neurology, Harvard Medical School, Chief of the Neurological Division, Boston City Hospital, formerly Neurologist to St Bartholomew's Hospital, London)

- (5) Munro,* Dr Donald, The Late Effects of Craniocerebral Injuries—A Consideration of the Criteria Necessary to Evaluate the Possible Causes, 117 Ann Surg (April 1943) 544, 23 B U L Rev (April 1943) —

(* F A C S, Surgeon-in-Chief for Neurological Surgery, Boston City Hospital, Asst Prof of Neurological Surgery, Harvard Med School, Assoc Prof of Neurological Surgery, Boston Univ Med School)

- (6) Solomon,* Dr Harry C and Smith, Dr Hubert Winston, Traumatic Neuroses in Court, 99 Am J Psychiat (May-June 1943) —, — L Rev, Summer, 1943

* Clinical Professor of Psychiatry, Harvard Med School, Chief of Therapeutic Research in the Boston Psychopathic Hospital, Visiting Neurologist to the Beth Israel Hospital, Boston, Assistant Visiting Neurologist to Massachusetts General Hospital, Boston)

- (7) Ebaugh,* Lt Col Franklin G and Brosin,** Major Henry W, Traumatic Psychoses, 18 ANN INT MED (April 1943) 666

(* Neuro-Psychiatric Consultant, VIII Service Command, A U S, Professor of Psychiatry, Univ of Colo Med School, Denver, Colo, and Director of Colorado Psychopathic Hospital—on leave of absence)

(** Chief, Neuro-Psychiatric Section, La Garde General Hospital, New Orleans, La, Asst Prof of Psychiatry, Univ of Chicago Med School, Chicago, Ill—on leave of absence)

- (8) Cobb,* Dr Stanley and Smith, Dr Hubert Winston, Relation of Emotions to Injury and Disease—A Call for Forensic Psychosomatic Medicine, 18 ANN INT MED, Aug 1943, 56 Harvard L Rev (Summer 1943))

(* Bullard Professor of Neuropathology, Harvard Medical School, Psychiatrist-in-Chief, Massachusetts General Hospital, Boston)

- (9) Merritt,* Dr H Houston and Solomon, Dr Harry C, Relation of Trauma to Syphilis of the Nervous System, 117 Ann Surg (April 1943) 623, 23 Boston U L Rev (April 1943) —

- (* Associate Professor of Neurology, Harvard, Assistant Visiting Neurologist, Boston City Hospital; Consulting Neurologist, Metropolitan State Hospital, Waltham, Mass., Consultant in Neuropsychiatry, U S District Court)
- (10) Pollock,* Dr Lewis J, Examination of Motor and Sensory Function as Related to Opinion Evidence, 1 Clinics (April 1943) 1424
 (* Professor of Nervous and Mental Diseases, Northwestern Univ., Chicago, Ill., Attending Neurologist to Passavant Memorial, Michael Reese and Wesley Memorial Hospitals, Chicago, Ill.)
- (11) Marble,* Dr Henry C, The Physician and the Workmen's Compensation Law, 1 Clinics (April 1943) 1441
 (* F A C S, Senior Surgeon and Chief of the Hand Clinic, Massachusetts General Hospital, Assistant in Surgery, Harvard Med School)
- (12) Schwartz,* Dr Louis, Problems of Proof in Claims for Recovery for Dermatitis, 18 ANN INT MED (April 1943) 500, 41 Mich L Rev (April 1943)—
 (* Fellow, Am Public Health Assn., Chief, Dermatoses Investigations Division, U S Public Health, Adjunct Professor in Dermatology, Georgetown Univ Med School, Lecturer, N Y U College of Medicine)
- (13) Homans,* Dr John, Circulatory Deficiency in the Extremities in Relation to Medico-Legal Problems, 18 ANN INT MED (April 1943) 518, 21 N C L Rev (April 1943)
 —
 (* Clinical Professor of Surgery, Emeritus, Harvard Med School)
- (14) Bennett,* Dr Granville Allison, Medical Criteria Which Govern Relations of Trauma to Joint Disease, 1 Clinics (April 1943) 1448
 (* Associate Professor of Pathology, Harvard Med School, As of May 1, 1943, Professor and Head of Department of Pathology in the Tulane Medical School, New Orleans)
- (15) Smith, Dr Hubert Winston and Bennett, Dr Granville Allison, Joint Disease in the Courts Select Problems of Proof, 18 Tenn L Rev (December 1943) —
- (16) Ober,* Dr Frank Roberts, Some Practical Criteria for Use in Forensic Orthopedic Cases, 1 Clinics (April 1943) 1476, 15 Rocky Mt. L Rev
 (* John B and Buckminster Brown Clinical Prof of Orthopedic Surgery, Harvard Med School, Chief, Orthopedic Dept., Children's Hospital, Boston, Orthopedic Surgeon, Peter Bent Brigham Hospital, Boston, Surgeon-in-Chief, New England Peabody Home for Crippled Children, President (1942-3) Am Orthopedic Assn.)
- (17) Aldrich,* Dr Robert Henry, Forensic Aspects of Burns, with Special Reference to Appraisal of Terminal Disability, 29 Va L Rev (April 1943) —, 117 Ann Surg (April 1943) 576
 (* Assistant in Surgery, Harvard Medical School)
- (18) Hertig,* Dr Arthur Tremain and Sheldon,** Dr Walter Herman, Minimum Criteria Required to Prove Prima Facie Case of Traumatic Abortion or Miscarriage, 117 Ann Surg (April 1943) 596
 (* Assistant Prof of Pathology and Associate in Obstetrics, Harvard Med School, Pathologist to the Boston Lying-In Hospital, Boston, Pathologist to Free Hospital for Women, Brookline, Mass.)
 (** Instructor in Pathology, Harvard Med School, Research Associate in Pathology, Boston Lying-In Hospital, Boston)
- (19) Joslin,* Dr Elliott P, Relation of Trauma to Diabetes, 117 Ann Surg (April 1943) 607, 15 Rocky Mt L Rev (April 1943) —
 (* Clinical Professor of Medicine, Emeritus, Harvard Med. School, Director of the George F Baker Clinic, Boston)
- (20) Warren* Dr Shields, Minimum Criteria Required to Prove Causation of Traumatic or Occupational Neoplasms (Cancer), 117 Ann Surg (April 1943) 585, 20 U of Chi L Rev (April 1943)
 (* Assistant Prof of Pathology, Harvard Med School, Pathologist to New England Deaconess Hospital, Harvard Cancer Commission New England Baptist Hos-

pital, Pondville State Hospital for Cancer, Director of State Tumor Diagnosis Service, Massachusetts, President, American Assn for Cancer Research)

- (21) Wolff,* Dr Harold G, Hardy,** James D, and Goodell,*** Helen, The Pain Threshold in Man, 99 Am J Psychiat (March-April 1943) —

(* Associate Prof of Medicine, Cornell Medical School, Staff, The New York Hospital, N Y City)

(** Ph D, Special Research Associate of Dr Wolff in experimental studies on the pain threshold in man)

(*** B S, Special Research Associate of Dr Wolff in experimental studies on pain threshold)

III FORENSIC PATHOLOGY

- (22) Leary,* Dr Timothy, How a Modern Medical Examiner's Office Functions in a Typical Investigation of "Sudden Death", Points of Superiority over Coroner's Office, 18 ANN INT MED (July 1943) —

(* Medical Examiner for Suffolk County, Mass, Lecturer in Legal Medicine, Harvard Med School)

- (23) Jetter,* Dr Walter W, When Can It Be Said That Death May Be Caused or Contributed to by Acute Alcoholism, 1 Clinics (April 1943) 1487

(* Instructor in Legal Medicine, Harvard Med School, Assistant in Neuropathology, Harvard Med School, State Pathologist, Mass Dept of Mental Health, Acting State Pathologist, Mass Dept of Public Safety, Member National Safety Council Committee for Standardization of Tests for Alcoholic Intoxication)

IV SCIENTIFIC CRIME DETECTION

- (24) Hoover,* J Edgar, The Scientific Crime Detection Laboratory, 1 Clinics (April 1943) 1503, 20 U of Chi L Rev (April 1943) —

(* Director, Federal Bureau of Investigation, U S Dept of Justice)

- (25) Wigmore,* Prof John H, Circumstantial Evidence in Poison Cases, 1 Clinics (April 1943) 1507, 23 B U L Rev (April 1943) —

(* Professor of Law and Dean Emeritus, Northwestern Univ Law School, Chicago, Ill)

- (26) Walker,* Dr Joseph, Scientific Evidence in Poisoning Cases, 1 Clinics (April 1943) 1520, 23 B U L Rev (April 1943) —

(* Instructor in Legal Medicine, Harvard Med School, Lt, Mass Police Force, Director, Chemical Laboratories, Mass Dept of Public Safety)

V MODES AND MECHANISMS OF SCIENTIFIC PROOF

- (27) Donaldson,* Dr Samuel W, Medical Facts that Can or Cannot be Proved by X-Ray, Historical Review and Present Possibilities, 18 ANN INT MED (April 1943) 535, 41 Mich L Rev (April 1943) —

(* Fellow, Am College of Radiology, Chairman, Medico-Legal Committee, Radiological Society of North America; Roentgenologist, St Joseph Mercy Hospital, Ann Arbor, Mich)

- (28) Riseman,* Dr Joseph E F, Principles of Electrocardiography, 15 Rocky Mt L Rev (April 1943) —, to be submitted for medical publication

(* Instructor in Medicine, Harvard Med School; Instructor in Medicine, Tufts College Med School, Associate in Medical Research and Associate Visiting Physician, Beth Israel Hospital, Boston)

- (29) Smith, Dr Hubert Winston and Riseman, Dr Joseph E F, Applied Use of the Electrocardiogram in Legal Proceedings, 15 Rocky Mt L Rev (April 1943) —, 18 ANN INT MED (July 1943)

- (30) Snyder,* Dr Lemoyne M, Criminal Interrogation with the Lie Detector, 15 Rocky Mt L Rev (April 1943) —; 18 ANN INT MED (April 1943) 551.

(* Medico-Legal Director of the Michigan State Police)

- (31) Boyd,* Dr William, Protecting the Evidentiary Value of Blood Group Determinations, 1 Clinics (April 1943) 1536, 17 So Calif L Rev (March 1943) —
 (* Associate Prof of Biochemistry, Boston Univ School of Medicine, Special Research Associate, Harvard University, Associate Member, Evans Memorial and Massachusetts Memorial Hospitals)
- (32) Maguire,* Prof John M, A Survey of Blood Group Decisions and Legislation in the American Law of Evidence, 1 Clinics (April 1943) 1560, 17 So Calif L Rev (March 1943) —
 (* Professor of Law, Harvard Law School, Asst Reporter, The American Law Institute's Committee on Evidence, which developed Model Code of Evidence)
- (33) Schoch,* Dr Magdalena, Determination of Paternity by Blood Grouping Tests The European Experience, 1 Clinics (April 1943) 1579, 17 So Calif L Rev (March 1943) —
 (* Formerly Assistant Prof of Law, Univ of Hamburg, now Research Assistant in Comparative Law, Harvard Law School)
- (34) Ladd,* Major Mason and Gibson,** Dr Robert B, Legal-Medical Aspects of Blood Tests to Determine Intoxication, 18 ANN INT MED (April 1943) 564, 29 Va L Rev (April 1943) —
 (* J A G D, U S Army, Prof and Dean, Univ of Iowa College of Law—on leave of absence, Member of the American Law Institute's Committee on Evidence, which developed Model Code of Evidence)
 (** Associate Professor of Biochemistry, State Univ of Iowa, Iowa City, Ia)

VI SCIENTIFIC PROOF AS A MEANS OF TESTING PREMISES UNDERLYING LEGISLATION OR LEGAL DOCTRINE

- (35) Rock,* Dr John, Medical and Biologic Aspects of Contraception Scientific Contradictions to Legal Restriction of Contraceptive Advice, 1 Clinics (April 1943) 1598, to be submitted for legal publication
 (* Instructor in Gynecology, Harvard Med School, Visiting Surgeon and Director of Fertility, Endocrine and Rhythm Clinics, Free Hospital for Women,
- (36) Myerson,* Dr Abraham, Certain Medical and Legal Phases of Eugenic Sterilization, 18 ANN INT MED (April 1943) 580, 53 Yale L J (April 1943) —
 (* Clinical Professor of Psychiatry, Harvard Med School, Professor (emeritus) of Neurology, Tufts College Medical School, Chief of Department of Neuropsychiatry, Beth Israel Hospital, Boston, Chairman, Committee on Research, American Psychiatric Association)

VII MEDICAL CRIMINOLOGY

- (37) Lennox,* Dr William Gordon, Amnesia Real and Feigned, 99 Am J Psychiat (March-April 1943) —, 20 U of Chi L Rev (April 1943) —
 (* Assistant Prof of Neurology, Harvard Med School, Visiting Neurologist, Boston City Hospital, Fellow, Am Psychiatric Assn, President, International League against Epilepsy)

VIII SOCIO-MEDICO-LEGAL PROBLEMS

- (38) Stearns,* Commander A. Warren, Medical and Social Factors in Crime, 18 ANN INT MED (April 1943) 599, 18 Ind L J (July 1943)
 (* Commander (MC) U S N R. on active duty, Professor of Psychiatry and Dean, Tufts College Medical School—on leave of absence)

IX SCIENTIFIC-LEGAL-MEDICAL CORRELATIONS

- (39) Hooton,* Dr Earnest Albert, Medico-Legal Aspects of Anthropology, 1 Clinics (April 1943) 1612, 15 Rocky Mt L Rev (April 1943) —
 (* Fellow A A A S, Royal Anthropological Institute and Am Academy of Arts and Sciences, Chairman, Dept of Anthropology of Harvard University, Curator of Somatology, Peabody Museum, Cambridge, Mass)

X HISTORICAL NOTES ON LAW-SCIENCE RELATIONS

- (40) Thayer,* Prof James, B Note on Poison in Roman Private Law, 1 Clinics (April 1943) 1625, 23 B U L Rev (April 1943) —
(* Professor of Law, Harvard Law School)
- (41) Polsky,* Samuel and Beresford,** Spencer, Some Probative Aspects of the Early Germanic Codes, Carolina and Bambergensis, 18 ANN INT MED (May 1943)—, 23 B U L Rev (April 1943) —
(* Student research assistant, in second year of Harvard Law School)
(** Formerly third year, Harvard Law School, and student research assistant, now Ensign, U S Navy)
- (42) Simboli,* David, Medico-Legal Vignettes, 1 Clinics (April 1943)
(* B A , Harvard 1940, Instructor in private school, New York State)

PART II

LAW-MEDICINE PROBLEMS AND LEGAL DOCTRINE

I EXPERT TESTIMONY AND JURIDICAL MECHANISMS

- (43) Morgan,* Prof Edmund M, Suggested Remedy for Obstructions to Expert Testimony by Rules of Evidence, 1 Clinics (April 1943) 1627, 20 U of Chi L Rev (April 1943) —
(* Royall Professor of Law, Harvard Law School, Cambridge, Mass , Reporter, The American Law Institute's Committee on Evidence, which developed Model Code of Evidence)
- (44) Pound,* Prof Roscoe, A Ministry of Justice as a Means of Making Progress in Medicine Available for Courts and Legislatures, 1 Clinics (April 1943) 1644, 20 U of Chi L Rev (April 1943)
(* Dean Emeritus, Harvard Law School, University Professor, Harvard, Cambridge, Mass)
- (45) Chafee,* Prof Zechariah, Jr, Privileged Communications Is Justice Served or Obstructed by Closing the Doctor's Mouth on the Witness Stand? 18 ANN INT MED (April 1943) 606, 53 Yale L J (April 1943) —
(* Langdell Professor of Law, Harvard Law School, Cambridge, Mass)

II PRIVATE LAW PROBLEMS OF INTEREST TO MEDICAL MEN

- (46) Dodd,* Prof Edwin Merrick, Jr, Contracts Not to Practice Medicine, 18 ANN INT MED (April 1943) 618, 23 B U L Rev (April 1943)—
(* Professor of Law, Harvard Law School, Cambridge, Mass)
- (47) Scott,* Prof Austin Wakeman, Tort Liability of Hospitals, 18 ANN INT MED (April 1943) 630, 17 Tenn L Rev (April 1943) 838
(* Dane Professor of Law, Harvard Law School, Cambridge, Mass)
- (48) Ludlam,* Warren, Plaintiff's Duty to Minimize Defendant's Liability by Surgery, 17 Tenn L Rev (April 1943) 821, to be submitted for medical publication
(* LL B Harvard Law School, January 1943, Associate of Baker, Botts, Andrews and Wharton, Attorneys and Counselors, Houston, Texas)
- (49) Smith, Hubert Winston, Legal Responsibility for Non-Therapeutic Surgery, to be submitted for medical publication
- (50) McCurdy,* Prof William Edward, Insanity as a Ground for Annulment or Divorce in English and American Law, 99 Am J Psychiat (May-June 1943) —, 29 Va L Rev (April 1943) —
(* Professor of Law, Harvard Law School, Cambridge, Mass)

- (51) Arthur,* Prof William R, Some Legal Aspects of the Use of Drugs, (Tentative title), 15 Rocky Mt L Rev (April 1943) —, to be submitted for medical publication.
(* Professor of Law, University of Colorado, Boulder, Colo)

III PUBLIC LAW PROBLEMS OF THE MEDICAL PROFESSION

- (52) Powell,* Prof Thomas Reed, Compulsory Vaccination and Sterilization, Constitutional Aspects, 18 ANN INT MED (April 1943) 637, 21 N C L Rev (April 1943)

—
(* Story Professor of Law, Harvard Law School, Cambridge, Mass)

- (53) Griswold,* Prof Erwin N, The Doctor's Federal Taxes, 18 ANN INT MED (April 1943) 647, 32 Calif L Rev (June 1943)—
(* Professor of Law, Harvard Law School, Cambridge, Mass)

REVIEWS

Advances in Pediatrics Vol 1 Edited by ADOLPH G DeSANCTIS, M D 306 pages, 23.5 × 16 cm Interscience Publishers, Inc, New York, N Y 1942 Price, \$4.50

Because it is difficult for physicians to keep abreast of pediatric literature, this book was written to present a few of the more important recent advances. It truly "is a collection of personalized monographs by outstanding authorities."

Subjects discussed are toxoplasmosis, virus diseases, chemotherapy, electroencephalography, vitamin K, ductus arteriosus, prematures, tuberculosis, and endocrinology.

This is a very fine book and well worth owning.

W M S

Laboratory Diagnosis of Protozoan Diseases By CHARLES FRANKLIN CRAIG, M D, M A (Hon), F A C S, F A C P, Col, U S Army (Retired), D S M 349 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia 1942 Price, \$4.50

This text embodies a comprehensive presentation of laboratory methods for the diagnosis of protozoan diseases. The following subjects are included: Amebiasis and other Intestinal Flagellates, the Leishmaniasis, Kala-Azar, Oriental Sore and Espundia, the Trypanosomiasis, east and west African type and Chagas' disease, Coccioidiosis, Malaria, and Balantidiasis. The accurate diagnosis of these diseases is dependent upon carefully performed laboratory tests. Much emphasis is placed on laboratory diagnostic methods which are discussed in great detail, clinical features are mentioned only briefly.

Each protozoan organism is analyzed by a consideration of the following points, namely: morphology, life cycle, collection and preparation of material for examination, staining methods, cultivation, serological tests and animal inoculation. The evidence presented in this analysis is evaluated, for each protozoan, in a section entitled "Critique of Diagnostic Methods." This is an expression of the subjective opinions of the author based upon forty years of personal experience in this field and is of great value to the reader.

The bibliography is ample and up to date, and there are many helpful illustrations and photomicrographs. The colored plates of the various malaria plasmodia are particularly well displayed.

This book will be of much value to anyone interested in protozoology or concerned with the diagnosis of these diseases.

E T L

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Sight Saver By C J GERLING 202 pages, 21 × 14 cm 1943 Harvest House, New York City Price, \$2.00

Pancreatic Function and Pancreatic Disease Studied by Means of Secretin By HENRIK O LAGFLOP, M D With a foreword by JOSEPH H PRATT, M D 289 pages, 23.5 × 15 cm 1943 The Macmillan Company, New York City Price, \$3.50

- Diseases of the Breast* By CHARLES F GESCHICKTER, M A, M D, with a special section on treatment in collaboration with MURRAY M COPELAND, A B, M D, F A C S 829 pages, 23.5 × 16 cm 1943 J B Lippincott Co, Philadelphia Price, \$10.00
- Essentials of Gynecology* By WILLARD R COOKE, M D, F A C S 474 pages, 23.5 × 16 cm 1943 J B Lippincott Co, Philadelphia Price, \$6.50
- Treatment of Fractures* By GUY A CALDWELL, M D, F A C S 303 pages, 24 × 16 cm 1943 Paul B Hoeber, Inc, New York City Price, \$5.00
- Bronchiectasis* By JAMES R LISA, B S, M D, and MILTON B ROSENBLATT, B S, M D 190 pages, 24 × 16 cm 1943 Oxford University Press, New York City Price, \$4.00
- Diagnostico Diferencial y Tratamiento de las Enfermedades Internas* Second Edition By RODOLFO DASSEN 774 pages, 25.5 × 17 cm 1943 El Ateneo, Buenos Aires
- Transactions of the Association of American Physicians* Vol LVII and Index volume of vols XXXI to LVI 334 pages (vol LVII), 287 pages (index volume), 23 × 15 cm 1943 Association of American Physicians
- Clinical Laboratory Diagnosis* By SAMUEL A LEVINSON, M S, M D, and ROBERT P MACFATE, Ch E, M S, Ph D 980 pages, 24 × 15.5 cm 1943 Lea and Febiger, Philadelphia, Pennsylvania Price, \$10.00
- The Antigonadotropic Factor with Consideration of the Antihormone Problem* By BERNHARD ZONDEK and FELIX SULMAN 185 pages, 23.5 × 16 cm 1943 Williams and Wilkins Co, Baltimore, Maryland Price, \$3.00
- Clinical Pediatrics* By I NEWTON KUGELMASS, M D, Ph D, Sc D 393 pages, 22 × 14.5 cm 1943 Oxford University Press, New York City Price, \$2.00
- Food Poisoning* By G M DACK, Ph D, M D 138 pages, 23.5 × 16 cm 1943 University of Chicago Press, Chicago, Illinois Price, \$2.00

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,321 Fellows and Associates of the College on active military duty. Herewith are reported the names of 44 additional members, bringing the grand total to 1,365.

Frank M. Acree

Orange V. Calhoun

Manley J. Capron

Charles J. Crawley

Francis R. Dieuaide

Orin J. Farness

Louis S. Faust

Stephen A. Foote, Jr.

James T. Gilbert, Jr.

John E. Greutter, Jr.

William H. Griffith

Joseph E. Haienski

Carl A. Hartung

R. Harold Jones

Donald S. King

Robert C. Kirk

Harry C. Kroon

Herman Lande

Joseph D. Landry

Robert W. Langley

Stephen L. R. Lirot

David W. McCarty

Francis E. McDonough

Julian E. McFarland

Roger S. Mitchell, Jr.

Hugh B. O'Neil

Frank Perlman

Carlos A. Pons

Lee T. Pruit

Lewis K. Reed

John M. Rice

David I. Rutledge

John C. Schlappi

S. Charlton Shepard

Donald G. Stannus

Irving E. Steck

Morris F. Steinberg

Russell A. Stevens

Harry E. Thompson

J. Lawn Thompson, Jr.

T. Noxon Toomey

Dwight L. Wilbur

Bernard P. Wolff

Joseph Ziskind

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College.

Dr. Roy Colonel Mitchell, Mt. Airy, N. C.

Dr. Jesse Dean Riley, State Sanatorium, Ark.

Dr. Vernon Cecil Rowland, Cleveland, Ohio

Dr. Frederick Slyfield, Seattle, Wash.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

- Dr James R Lisa, F A C P, New York, N Y—"Bronchiectasis",
 Dr Harry R Litchfield, F A C P, Brooklyn, N Y—"Therapeutics of Infancy and Childhood," Vol I,
 Dr Franklin B Peck, F A C P, Indianapolis, Ind—"Diabetes Abstracts," 1942 edition

Reprints

- Dr William A D Anderson (Associate), St Louis, Mo—13 reprints,
 Dr George E Baker, F A C P, Casper, Wyo—2 reprints,
 Dr Robert S Berghoff, F A C P, Chicago, Ill—1 reprint,
 J Edward Berk, F A C P, Captain, (MC), U S Army—1 reprint,
 Dr Leon L Blum (Associate), Terre Haute, Ind—5 reprints,
 Dr Ralph O Clock, F A C P, Brooklyn, N Y—1 reprint,
 Dr Charles F De Garis, F A C P, Oklahoma City, Okla—2 reprints,
 Dr Elliott B Edie, F A C P, Uniontown, Pa—1 reprint,
 Dr Guy H Faget, F A C P, U S Public Health Service, Carville, La—1 reprint,
 Donald E Forster, F A C P, Captain, (MC), U S Army—1 reprint,
 Joseph J Furlong, F A C P, Lieutenant, (MC), U S Army—2 reprints,
 Dr Mayer A Green (Associate), Pittsburgh, Pa—1 reprint,
 Dr Lynn T Hall, F A C P, Omaha, Nebr—3 reprints,
 Dr John N Hayes, F A C P, Saranac Lake, N Y—3 reprints,
 Dr William E Jahsman, F A C P, Ferndale, Mich—1 reprint,
 Dr John J Weber, F A C P, Brooklyn, N Y—1 reprint,
 Dr Willard R Wirth, F A C P, New Orleans, La—1 reprint

Dr Theodore J Abernethy (Associate), Washington, D C, is now a member of the Commission on Acute Respiratory Diseases, and is stationed at Fort Bragg, N C He is devoting his full time to research on respiratory diseases in the Army

The American College of Chest Physicians, through its Board of Regents, has announced the cancellation of its 1943 Annual Session

The Executive Board of the American Public Health Association has announced that a Wartime Public Health Conference and the 72nd Annual Business Meeting of the Association will be held in New York, N Y, October 12-14, 1943 The program will be devoted exclusively to wartime emergency matters as they affect public health and the public health profession

The 4th International Assembly of the International College of Surgeons will be held in New York, N Y, June 14-16, 1943 The program will be devoted to war surgery and rehabilitation

The American Urological Association has announced the cancellation of its 1943 meeting The Association also announced that the Five Hundred Dollar Research Prize offered annually will not be awarded this year

Leon H Warren (Associate), Major, (MC), U S Army, spoke on "Military Dermatology" in connection with a series of lectures on the professional aspects of military medicine conducted at George Washington University School of Medicine on February 5, 1943

At the invitation of the Governor of the Territory of Hawaii, Dr George Baehr, F A C P, Chief Medical Officer, Office of Civilian Defense, Washington, D C, recently conferred with local authorities on civilian defense activities. Defense activities of the islands are being reorganized now that the government is in the process of being transferred from Army to civil authorities.

On February 24, 1943, Dr Baehr spoke at the War Conference of the California Hospital Association held in Berkeley, Calif, on "Recent Observations in England and Scotland" and "Hospital Participation in the Emergency Medical Service"

On February 26, 1943, Paik, Davis & Company, Detroit, Mich, was awarded the Army-Navy "E" for excellence in the production of materials for saving lives. The "E" pennant was presented to Dr A W Lescohier, President of the Company, by John M Willis, F A C P, Brigadier General, (MC), U S Army, Commanding General at Camp Grant, Ill.

Honored guests at the presentation ceremony included Dr Bruce H Douglas, F A C P, Health Commissioner of the City of Detroit, and Dr Warren B Cooksey, F A C P, Medical Director of the Detroit Section of the American Red Cross.

Dr B Earl Clarke, F A C P, Providence, R I, recently spoke on "The History of the Microscope and Early Microscopy" at a meeting of the Penobscot County Medical Association in Bangor, Maine.

On January 4, 1943, Dr Joseph Yampolsky, F A C P, Atlanta, Ga, was awarded the L C Fischer award of One Hundred Dollars for the best written paper presented before the Fulton County (Ga) Medical Society during the past year. The award, which was presented by Dr Allen H Bunce, F A C P, Atlanta, was given Dr Yampolsky for his work on "Syphilitic Aortitis in a Nine Year Old Child."

Dr E Perry McCullagh, F A C P, Cleveland, Ohio, spoke on "Male Sex Hormone" at a meeting of the Allegheny County Medical Society in Pittsburgh, Pa, January 19, 1943.

The U S Army General Hospital at Temple, Tex, has been named the McCloskey General Hospital in honor of James A McCloskey, Major, (MC), U S Army, the first regular Army medical officer to lose his life in the present war with Japan. The McCloskey General Hospital, which was opened October 20, 1942, has a capacity at present of 1,500 beds, and is equipped to handle all types of cases.

Sloan G Stewart (Associate), Major, (MC), U S Army, has been named Chief of Medicine.

Dr George S Bond, F A C P, Indianapolis, spoke on "Criteria in the Evaluation of Abnormal Hearts" at a two-day conference on industrial health conducted in Indianapolis, February 25-26, 1943, by the Committee on Industrial Health of the Indiana State Medical Association.

Dr Andrew C Woofert, F A C P, has been assigned by the U S Public Health Service to Iowa to direct the venereal disease program in that State during the war period.

Dr Raymond Hussey, F A C P , Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md , has been appointed Scientific Director of the new Army Industrial Hygiene Laboratory at Johns Hopkins University School of Hygiene and Public Health

Dr Andrew P Biddle, F A C P , Detroit, Mich , has been elected President of the Detroit Library Commission

Dr Elmer E Glenn, F A C P , Springfield, Mo , was recently named President of the Missouri Tuberculosis Association

Dr Ellen C Potter, F A C P , Trenton, N J , has been appointed Director of Medicine and Chairman of the Child Care Committee of the Office of Civilian Defense Director of the State of New Jersey

Dr Russell L Cecil, F A C P , New York, N Y , has been named President of the New York Rheumatism Association This Association was formally organized January 22, 1943, to "unite physicians in New York and environs who are interested in arthritis and rheumatic disorders, to improve the treatment of patients with arthritis, particularly those attending the arthritis clinics in Greater New York, and to stimulate research on these disorders"

Dr Raymond L Gregory, F A C P , has accepted an appointment as Professor of Medicine and Director of the Outpatient Clinic, and Continuation Courses at the University of Texas Medical Branch, Galveston

On February 11, 1943, Dr L Maxwell Lockie, F A C P , Buffalo, N Y , lectured on "The Management of Arthritis, Acute and Chronic," and on February 23, Dr Clayton W Greene, F A C P , Buffalo, lectured on "Renal Lesions Simulating Other Maladies" before the Madison County Medical Society in Oneida, N Y These lectures were arranged by Dr Greene under the auspices of the Medical Society of the State of New York as postgraduate instruction on the treatment of common diseases

Dr C Lydon Harrell, F A C P , Norfolk, Va , was named President of the Seaboard Medical Association at its annual meeting in Wilson, N C , December 1-3, 1942

James O Gillespie, F A C P , Colonel, (MC), U S Army, has been awarded the Distinguished Service Medal for "developing hospitals on Bataan Peninsula with only extremely limited personnel and equipment" Colonel Gillespie was Chief of the Medical Service at the Sternberg General Hospital in Manila at the outbreak of the war He is now a prisoner of war

On March 26, 1943, Dr Lloyd F Craver, F A C P , New York, N Y , delivered the 19th Ludwig Hektoen Lecture of the Frank Billings Foundation under the auspices of the Institute of Medicine of Chicago Dr Craver discussed "The Diagnostic Problems of Early Cancer"

The New Orleans (La) Graduate Medical Assembly held its 7th Annual Assembly, March 15-18, 1943 The program included lectures clinics, symposiums,

scientific and technical exhibits, medical motion pictures and round table luncheons. Among the Fellows of the College who participated were Dr Tinsley R Harrison, Winston-Salem, N C, Dr Louis Hamman, Baltimore, Md, Dr Howard T Karsner, Cleveland, Ohio, and Lieutenant Colonel Edgar V Allen, (MC), U S Army

On February 15, 1943, Edgar E Hume, F A C P, Colonel, (MC), U S Army, delivered the 22nd Annual Beaumont Lecture at a meeting of the Wayne County Medical Society, Detroit, Mich. Colonel Hume spoke on "Contributions of U S Army Medical Officers to Science"

At the annual meeting of the Federation of State Medical Boards held in Chicago, Ill, February 16, 1943, Dr Frank M Fuller, F A C P, Keokuk, Iowa, was inducted into the Presidency. Dr Walter L Bierring, F A C P, Des Moines, Iowa, was reelected Secretary-Treasurer

At the annual meeting of the American Foundation for Tropical Medicine, Inc, New York, N Y., January 19, 1943, Thomas T Mackie, F A C P, Lieutenant Colonel, (MC), U S Army, was elected President of the Foundation and Dr Willard C Rappleye, F A C P, New York, N Y, Vice President

The Chamber of Commerce of the United States recently announced the creation of a National Health Advisory Council to consider national health problems in connection with the war program. Dr James S McLester, F A C P, Professor of Medicine, University of Alabama School of Medicine, Birmingham, was named General Chairman of the Council. Among the other Fellows of the College who have been named members of the Council are

Dr James E Paullin, Atlanta, Ga
 Dr George Morris Preisol, Philadelphia, Pa
 Dr Russell M Wilder, Rochester, Minn
 Dr Joseph C Doane, Philadelphia, Pa
 Dr Louis Hamman, Baltimore, Md
 Dr Wallace M Yater, Washington, D C
 Dr Arthur F Chace, New York N Y
 Dr Paul D White, Boston, Mass
 Dr J Burns Amberson, Jr, New York, N Y
 Dr Felix J Underwood, Jackson, Miss
 Dr Harry E Ungerleider, New York, N Y

Ross T McIntire, F A C P, Rear Admiral, (MC), U S Navy, The Surgeon General, received the honorary degree of Doctor of Science at the commencement exercises of Marquette University School of Medicine, Milwaukee, Wis, February 13, 1943

Dr Samuel M Poindexter, F A C P, Acting College Governor for Idaho, Boise, was recently appointed a member of the Idaho State Board of Medical Examiners

The Medical College of Virginia conducted a symposium on "Nutrition," March 25-27, in Richmond, Va. Among those who participated in the program were Dr William H Sebrell, Jr, F A C P, U S Public Health Service, Bethesda, Md, and Dr Virgil P Sydenstricker, F A C P, Augusta, Ga

Dr Robert Chobot, F A C P, New York, N Y, was recently elected President of the Society for the Study of Asthma and Allied Conditions and Dr Will Cook Spain, F A C P, New York, N Y, was reelected Secretary

The American Association of Industrial Physicians and Surgeons, the American Industrial Hygiene Association and the National Conference of Governmental Hygienists will hold a joint four-day "War Conference" in Rochester, N Y, May 24-27, 1943. Among the problems that will be discussed from a practical standpoint are the mass entry of women into industry, older-age employees, with their various associated problems, proper placement and employability considerations of the 4F rejectees, rehabilitation and proper employment of those already discharged from the military services because of disabling conditions, toxic and other hazards from new substances, new processes, and the use of substitute materials, absenteeism, fatigue, nutrition, effects of long hours, double shifts, two-job workers, overtime, increased industrial accident rates, advances in the treatment of illnesses and injuries, and many others

Lt Col H L Quickel, (MC), U S A, Retired, on March 15 assumed the duty of Senior Examining Physician (chest) with the North Carolina State Board of Health at Raleigh, N C

SCHEDULE OF FUTURE REGIONAL MEETINGS

Multi-State Regional Meetings for the duration of the War will take the place of the customary Annual Session. Already such meetings have been held in Philadelphia, in Chicago, in Boston and in New Orleans. These have met with universal favor and satisfaction. The attendance has averaged 40 per cent of the membership in the States represented, with a very large representation of guest attendants from the Army, Navy and Public Health Service. Programs are streamlined and carefully organized on subjects of the greatest importance and interest in these times, not only to civilian physicians, but to Medical Officers in our Armed Forces.

The customary program is an all-day session, concluding with an evening dinner-meeting, addressed by the President and other Officers of the College, and by high ranking Medical Officers and authorities from the Armed Forces. These meetings require but a minimum of lost time from practice or from active duty, and they afford not only an inspiring day of postgraduate work, but a welcome respite from strenuous and continuous work. The regional character of the meetings reduces the amount of travel, and the shortness of the sessions makes minimum demand upon hotel and meeting facilities.

Schedule

- Washington (Delaware, District of Columbia, Maryland, North Carolina, Virginia and West Virginia), April 24, 1943
Dr Wallace M Yater, Washington, Governor for the District of Columbia, *General Chairman*
- Great Falls (Montana and Wyoming), May 1
Dr E D Hitchcock, Great Falls, Governor for Montana, *General Chairman*
- Kansas City (Kansas, Missouri, Nebraska and Oklahoma) May 8
Dr A C Griffith, Kansas City, Third Vice President, *General Chairman*

- Columbus (Kentucky, Ohio, Western Pennsylvania and West Virginia), May 14
 Dr A B Brower, Dayton, Governor for Ohio, *General Chairman*,
 Dr Charles A Doan, Columbus, *Local Chairman*
 Jacksonville (Alabama, Florida, Georgia and South Carolina), May (?)
 Dr T Z Cason, Jacksonville, Governor for Florida, *General Chairman*
-

SPECIAL NOTICE

THE RESEARCH COUNCIL ON PROBLEMS OF ALCOHOL

ANNOUNCE A \$1,000 AWARD

FOR OUTSTANDING RESEARCH ON ALCOHOLISM DURING 1943

1 The research for which the award will be granted must contribute new knowledge, in some branch of medicine, biology, or sociology, important to the understanding or prevention or treatment of alcoholism

2 Any scientist in the United States, Canada or Latin America is eligible for the award

3 The project may have been inaugurated at any time in the past or during the year 1943, provided (a) that a substantial part of the work be carried on during the year 1943, (b) that it be developed to a point at which significant conclusions are possible before the end of the year, and (c) that a report on the work has not been previously announced and described before a scientific body or previously published

4 It is desirable, but not necessary, that those planning to work for the award send to the Council before March 1, 1943, a statement of such intention. If the Council receives such information, it can be helpful in the prevention of undesirable duplication of effort. If a research project is conceived and inaugurated later in the year 1943, a statement of intention may be sent to the Council at a later date.

5 A report on the work and resulting conclusions must be submitted to the Research Council on Problems of Alcohol on or before February 15, 1944. The Council will provide an outline for use in the preparation of reports.

6 The award will be in cash, and will be given to an individual scientist whose work is judged sufficiently outstanding and significant to merit the award.

7 The Committee of Award will consist of five persons—an officer of the American Association for the Advancement of Science, and four representatives of the Scientific Committee of the Research Council on Problems of Alcohol.

8 If the Committee is not convinced of the outstanding merit of the research done during 1943, as described in reports submitted, it may, at its discretion, postpone the award until another year, or until such time as work of such merit has been performed.

The Council will send on request, to any scientist, an outline of basic policies governing its research program, lists of Council studies (completed, under way and contemplated), and information regarding the studies of other agencies.

Scientists planning to do research in connection with the award may send a statement of intention to The DIRECTOR, THE RESEARCH COUNCIL ON PROBLEMS OF ALCOHOL, Pondfield Road West, Bronxville, New York.

A C P REGIONAL MEETING

COLUMBUS, MAY 14, 1943

A Regional Meeting of the American College of Physicians for the States of Kentucky, Ohio, West Virginia and Western Pennsylvania will be held in Columbus, Friday, May 14, with headquarters at the Neil House. The meeting is sponsored by the College Governors for those States, Dr Chauncey W Dowden, Louisville, Governor for Kentucky, Dr A B Brower, Dayton, Governor for Ohio, Dr Albert H Hoge,* Bluefield, Governor for West Virginia, Dr R R Snowden, Pittsburgh, Governor for Western Pennsylvania. Dr Brower is the General Chairman and Dr Charles A Doan of Columbus is the Chairman of Local Arrangements.

The scientific program will open at 10 00 a m at the Neil House and except for a luncheon intermission, will continue through the day to 5 00 p m. A concluding dinner meeting will be held in the evening when a number of distinguished guests will make brief addresses among whom will be Dr James E Paullin, President, Atlanta, Ga, Lt Col F Dennette Adams, Columbus, Medical Consultant to the Fifth Service Command and official envoy of the Surgeon General of the U S Army, Comdr Edward L Bortz, Philadelphia, Chairman of the Committee on War-Time Graduate Medical Meetings and envoy of the Surgeon General of the U S Navy, Brigadier General Eugen G Reinartz of the School of Aviation Medicine, Randolph Field, Tex, Edward R Loveland, Executive Secretary of the College, Philadelphia.

The tentative program follows

(Topic not yet announced) Eugen G Reinartz, F A C P, Brigadier General, (MC), U S A, School of Aviation Medicine, Randolph Field, Tex

"The Atypical or Virus Pneumonia" Bruce Kenneth Wiseman, F A C P, Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

"Some Clinical Aspects of Epidemic Meningococcus Infections" F Dennette Adams, F A C P, Lt Col, (MC), U S A, Medical Consultant, Fifth Service Command, Fort Hayes, Columbus, Ohio

"Recent Trend on Experiment and Theory on the Influence of Training on Some Visual Function" Samuel Renshaw, Ph D (by invitation), Professor of Experimental Psychology, Ohio State University, Columbus, Ohio

"Industrial Medical Problems in War Production" T Lyle Hazlett, F A C P, Professor of Industrial Medicine, University of Pittsburgh School of Medicine, Medical Director, Westinghouse Electric & Manufacturing Co, Pittsburgh, Pa

"The Problem of Tuberculosis in Apparently Healthy Man as Shown in the Routine Examinations for Induction into the Armed Forces" C Howard Marcu, F A C P, Associate Professor of Medicine, University of Pittsburgh School of Medicine, Medical Director, Tuberculosis League of Pittsburgh, Pittsburgh Pa

"Traumatic Lesions of the Heart" Edward J McGrath (by invitation), Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio

(Topic not yet announced) Roy W Scott F A C P, Professor of Clinical Medicine, Western Reserve University School of Medicine Physician-in-Chief, City Hospital, Cleveland, Ohio

* Deceased, April 9, 1943

- "Endocrine Regulation of Growth" Willard O Thompson, F A C P, Associate Clinical Professor of Medicine, Rush Medical College, Chicago, Ill
- "Clinical Endoscopy Studies of the Tracheal Tree" Maurice G Buckles, F A C P, Instructor in Medicine, University of Louisville School of Medicine, Louisville, Ky
- "Mineral Metabolism" Zolton T Wirtschafter (Associate), Major, (MC), U S A, Chief, Section of Civilian Medicine and Industrial Hygiene, Wright Field, Dayton, Ohio
- "Deficiency Diseases in Relationship to the Nervous System" Charles D Aring (by invitation), Associate Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
- "The National History of Tuberculous Tracheal Bronchitis" David Salkin, F A C P, Instructor in Medicine, West Virginia University School of Medicine; Medical Director, Hopemont Sanitarium, Hopemont, W Va

OBITUARIES

DR OLIVER M LAYTON

Dr Oliver M Layton, F A C P, Fond du Lac, Wisconsin, was born January 20, 1871, and died on December 27, 1942. He received his medical degree from Rush Medical College in 1895. He engaged in the practice of medicine in Metropolis, Michigan for a period of five years. In 1901 Dr Layton came to Fairwater, Wisconsin. He was also a registered Pharmacist in Fairwater. He continued his practice in Fairwater until 1912 at which time he returned to the Rush Medical College for postgraduate study. He returned to Fond du Lac, Wisconsin, in 1916 where he engaged in the practice of Internal Medicine until the time of his death.

Dr Layton became a member of the Wisconsin State Medical Society in 1916. He was an active member of the Fond du Lac County Medical Society, acting first as Secretary of the organization and in 1920 he was elected President of the society. He was elected a Fellow of the American College of Physicians in 1920.

During the World War I, Dr Layton was a member of the Medical Reserve. He served as Medical Director of the District Advisory Board of the American Red Cross. He was appointed as Medical Director of the St Agnes School of Nursing at Fond du Lac, Wisconsin. Dr Layton was an earnest student of medicine, devoted to his patients and was held in high esteem by his fellow practitioners. He was active in civic affairs and devoted much time to teaching in the school of nursing and instructing in the Red Cross.

Dr Layton died suddenly from coronary thrombosis on December 27, 1942. He is survived by his wife, one son and two daughters. His many grateful patients, as well as his brother practitioners, mourn his passing.

ELMER L SEVRINGHAUS, M D, F A C P,
Governor for Wisconsin

DR PETER WHITMAN ROWLAND

Dr Peter Whitman Rowland, Jr, one of Memphis' leading physicians died suddenly January 10, 1943, while at work. He was born January 23, 1893, at Coffeerville, Miss. He received his B S degree from the University of Mississippi in 1912, and his degree in medicine from the University of Virginia in 1919.

He was Assistant Professor of Bacteriology and Pathology at the University of Mississippi during 1920 and 1921, and Assistant Professor of Medicine in the University of Tennessee from 1930 to 1940.

He had been a Fellow in the American College of Physicians since 1928. He was a member of the Memphis and Shelby County Medical Society, the Tennessee State Medical Association, the Southern Medical Association

the American Medical Association, and a Diplomate of the American Board of Internal Medicine

Dr Rowland was an intense and profound student of medicine, especially interested in diseases of the cardiovascular system and diabetes mellitus

He leaves a very distinguished father who has taught in the Medical School of the University of Mississippi for 41 years; his wife, Mrs Jane Taliaferro Rowland, and a son, Peter Whitman Rowland III

WILLIAM CALVERT CHANEY, M D , F A C P ,

Governor for Tennessee .

DR FRED HERMAN KRUSE

Dr Fred Herman Kruse, F A C P , was born in Kentucky, June 30, 1879; he died at his home, in San Francisco, January 14, 1943

Dr Kruse spent his early life in California and became a teacher in the public schools before entering upon the study of medicine. He received the degree of B S in 1913 and M D in 1915 from the University of California. In 1915 and 1916 he served a medical internship at the University of California. With the exception of the following year, during which he was a Medical Resident at the Johns Hopkins Hospital, Baltimore, Dr Kruse maintained an active teaching and visiting connection with the Medical School and Hospital of the University of California. At the time of his death, and for some years before, he was Clinical Professor of Medicine and Chief of the Gastro-enterology Clinic. He was also a member of the Staff of the Franklin Hospital in San Francisco.

Dr Kruse belonged to the San Francisco County Medical Society, California State Medical Association, the California Academy of Medicine and American Gastro-enterological Association. He was a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1931, Diplomate, American Board of Internal Medicine.

As a diagnostician and consultant, Dr Kruse enjoyed a well-earned reputation on the Pacific Coast. His services were in constant demand and he was never too busy nor too tired to devote meticulous care and much thought to the diagnostic problems of his patients. Gifted with a friendly, sympathetic personality, he was able to achieve much in his career that scientific medicine alone would scarcely have accomplished. Modest and self-sacrificing, he was entirely devoted to family, friends, students and patients.

ERNEST H FALCONER, M D , F A C P ,

Governor for Northern California

DR WILLIAM BYRNE BROWN

Dr William Byrne Brown, F A C P , Director of the Division of Health Education at Stephens College, Columbia, Mo , died suddenly, November 8, 1942, of heart disease. He was born in Webster, W Va , August 2, 1904

He received his A B degree from West Virginia University in 1927 and his B S degree in medicine from the same institution in 1933. He graduated from Rush Medical College, Chicago, in 1934 and received his degree after an internship at St Luke's Hospital in that city. In September, 1936, he went to Stephens College as Resident Physician in the Division of Health Education, and in June, 1939, upon the retirement of Dr Frank G Nifong, Dr Brown succeeded to the Directorship of Health Education, which position he held at the time of his death.

Dr Brown took an active part in the activities of the American Student Health Association, holding the office of Chairman of the Committee on Organization and Administration at the time of his death. He was a member of the Boone County Medical Society (President, 1941), a member of the Missouri State Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1941.

RALPH A KINSELLA, M D, F A C P,
Governor for Missouri

DR HERBERT ELDRIDGE MILLIKEN

Dr Herbert Eldridge Milliken died as the result of myocardial infarction at Portland, Maine February 9, 1943. His final illness was a recurrence of a disease which had forced his retirement from practice four years earlier.

Dr Milliken was born in Surry, Maine, January 25, 1880. He was graduated from Bowdoin Medical School in 1901 and served as house officer at the Maine General Hospital in Portland and the Rhode Island State Hospital in Providence. He practiced for a year in Northeast Harbor, Maine, then moved to Waterville where he remained until 1910. On the latter date he removed to Portland and continued his practice there for the remainder of his life. In 1912 he left for a year of study in Vienna. On his return to Portland, Dr Milliken restricted his practice to internal medicine.

As an officer in the Medical Reserve Corps, United States Army, during World War I, Dr Milliken was at first in charge of the Gastro-enterological Service at the Base Hospital at Camp Dodge, Iowa. He was later transferred to Camp Greene, North Carolina to serve as lecturer and instructor in physical diagnosis during the mobilization period. He was ordered overseas August 14, 1918 served with Base Hospital 54 and later was made Chief of Medical Service of Unit 8, a post which he held until his discharge from the service July 31, 1919. He then continued the practice of internal medicine in Portland for the next twenty years.

Dr Milliken was elected to Fellowship in The American College of Physicians in 1927. He was a member of the American Medical Association, the Maine Medical Association, the Cumberland County Medical Society, the Portland Medical Club and the Maine Historical Society. He

was Consultant in Internal Medicine, U S Public Health Service and held a commission as Lieutenant Colonel, Medical Reserve Corps, United States Army For many years he was a member of the medical staff of the Maine General Hospital He served as instructor in physical diagnosis at the Bowdoin Medical School from 1913 to 1917

Dr Milliken will be remembered, alike by colleagues and by patients, as a thoughtful, studious physician, whose decisions were made only after thorough investigation and careful deliberation

E H DRAKE,
Governor for Maine

DR ERNEST BORING PORTER

Dr Ernest Boring Porter, F A C P , of Altadena, California, died of coronary thrombosis on November 15, 1942

Dr Porter was born in New Jersey on February 26, 1895 He received his B S degree in 1924 and graduated in 1925 as Doctor of Medicine from Northwestern University Medical School

For the first four years of his brief medical career he was associated with Dr James F Churchill of San Diego, from whom he gained much knowledge of Internal Medicine From 1925 to 1934 he was a Member of the Staff of the Mercy Hospital, San Diego, at which institution he attained the position of Chief of Staff for one year During the same period he served on the medical staff of the Scripps Metabolic Hospital and the San Diego County General Hospital, where he was Chief of Staff for two years Dr Porter was a member of the San Diego Medical Society, the California Medical Association and a Fellow of the American Medical Association In 1938 he became a Fellow of the American College of Physicians

A few years ago failing health compelled him to retire from active practice, and his untimely death at the age of forty-seven brought a close to a most promising career in the field of Internal Medicine

ROY E THOMAS, M D , F A C P ,
Governor for Southern California

ANNALS OF INTERNAL MEDICINE

VOLUME 18

MAY, 1943

NUMBER 5

CANCER OF THE STOMACH· WITH SPECIAL REFERENCE TO EARLY DIAGNOSIS *

By I W HELD, M D , F A C P , and IRVING BUSCH, M D , F A C S ,
New York, N Y

THE small percentage of five year survivals following operative intervention in cases of carcinoma of the stomach has been very discouraging. The aim of all diagnostic methods has, therefore, been to establish an early diagnosis. Nevertheless, only between 30 and 40 per cent of cases of resectable cancer of the stomach are submitted to the surgeon. Patients with cancer who never reach the operating table are in one of two categories. The cancer is either of such a malignant nature that it spreads very rapidly to the neighboring glands and organs, or to distant structures, or the growth has invaded a silent area of the stomach, remaining asymptomatic. Such a patient presents himself for treatment when the lesion has already reached an inoperable stage.

From our clinical experience, it seems appropriate to divide cancer of the stomach into two groups. The first group comprises those cases in which the cancer starts on a perfectly healthy gastric mucous membrane. In the second group the cancer develops on a previously diseased mucous membrane.

In the first group are approximately 70 per cent of all the cases. In reality, the patient will often volunteer the information that he has had an iron clad stomach and could digest everything. Though most of these patients are above the age of 50, the cancer may occur in younger individuals, and even before the age of 20. The younger the individual, the more malignant the growth.

When the cancer affects the silent area of the stomach (the greater curvature of the pars media or the lesser curvature) involving more of the anterior wall than the posterior wall, gastric motility is usually not interfered with. Consequently the patient does not present himself until a good sized palpable mass can be detected in the epigastrium. The subjective symptoms are extremely vague, consisting of epigastric distress, belching,

* Received for publication February 19, 1942

Copyright, 1943, by The American College of Physicians

fullness in the epigastrium, loss of appetite, coated tongue and dryness of the mouth. There may be only moderate loss of weight, especially if the symptoms are of a few weeks' duration. Gastric acidity may be normal, although occasionally there is sub- or even anacidity. Normal acidity should not in-



FIG 1 Hour glass stomach due to carcinoma of the pars media

fluence the diagnosis. In younger individuals, particularly in the rare cases of cancer of the stomach occurring before the age of 30, all the clinical evidence of cancer can exist despite a perfectly normal acidity.

When the cancerous lesion involves the posterior wall of the pars media, pain in the epigastrium radiating to the back is a prominent symptom. The

pain is often excruciating, and is worse at night, necessitating the administration of narcotics. The greater the involvement of the posterior wall, the less accessible is the lesion to palpation.

If the cancer invades the entire anterior and posterior walls of the pars media, the characteristic cancer hour glass stomach is produced (figure 1)



FIG 2 Hour glass stomach due to ulcer on lesser curvature

The edges of the constricted portion are irregular, and the canal between the upper and lower part of the hour glass is centrally situated, in contradistinction to the canal of hour glass due to ulcer (figure 2), in which case the connecting canal is on a line with the lesser curvature of the stomach. Furthermore, as seen in the figures, in cancer hour glass stomach the upper sac fills only partially with barium and, therefore, is smaller than the lower

sac which is more completely filled. This is due to the rigidity of the canal which permits the barium to rush through. On the other hand, in the ulcer hour glass, the connecting canal between the two sacs is usually spastic and inhibits passage of the barium meal. The upper sac, therefore, contains the greater part of the barium meal. In some cases in which there is a stenosing ulcer of the pylorus and an ulcer of the lesser curvature of the stomach, the hour glass will show the lower sac to be half-moon shaped and larger than the upper sac (figure 3)



FIG 3 Stenosing ulcer of pylorus and ulcer of lesser curvature, producing hour glass stomach, the lower sac half-moon shaped (Stomach photographed from left to right)

If the cancer develops at the next most common site, namely at the prepyloric region, and if it is not the rare annular type which invades the lumen of the pylorus, motility disturbances are absent. Such patients have insufficient subjective symptoms to present themselves for early treatment. When seen they have a large, tender, freely movable, palpable tumor in the epigastric region, and to the right of the median line. In these cases there is subacidity or anacidity.

Cancer of the pyloric region usually develops later in life than does cancer of the pars media, and is often very insidious in onset. The symptoms are very vague, consisting primarily of loss of appetite, with a marked dislike for meats. A patient in his late forties or fifties who previously had no digestive disturbances, presenting himself with such symptoms, even if the acidity is normal, should be subjected to a very careful roentgenologic

and gastroscopic examination in order that the cancer in its earliest stage should not be overlooked

The rapid passage of food into the duodenum visualized roentgenologically is an important finding in early cases of pyloric cancer. The pylorus presents a rigid tube which, however, is not irregular, so that unless the roentgenologist knows the clinical history, he may be unable to make a diagnosis of cancer from the roentgen-ray examination alone. We adhere to the teaching of Holzknicht¹ as to the diagnosis of a scirrhus carcinoma of the pylorus in previously healthy middle aged or elderly individuals. The essence of his observations as early as 1910 is the following. The outstanding symptoms leading to such a diagnosis are subacidity or anacidity, a rigid pylorus through which food passes with extraordinary rapidity in the early part of digestion, incomplete emptying of the stomach after four or five hours, and diminished or absent peristaltic waves in the pyloric region and a conspicuous absence of antral contraction. We are in accord with Holzknicht that such cases should be given the benefit of surgical intervention. It is quite true that occasionally this type of pylorus might be due to a chronic pyloritis, so that resection may only reveal the presence of an inflammatory lesion, but in the majority of cases one is rewarded by having diagnosed cancer in the resectable stage.

The rapid passage of food during the early part of digestion is due to the fact that the sphincter pylori has not been invaded by the lesion and is patent. This may be compared to carcinoma of the rectum in which case the sphincter ani acts in a similar manner, or to cancer in the lower end of the esophagus in which passage of food into the stomach is not disturbed although there is accumulation of food in the esophagus proper and dilatation of the esophagus due to atony of the organ.

Disturbed motility is an early phenomenon if the lumen of the pylorus is invaded by an annular carcinoma. Subacidity is the rule, and lactic acid is also present if there is marked gastric stasis. Epigastric pain, relieved by spontaneous or induced vomiting, is frequent in these cases (figure 4).

Occasionally the cancer invades exclusively the posterior wall and lesser curvature of the stomach. Characteristic symptoms are persistent pain in the lower dorsal and epigastric region, frequent vomiting of bile stained gastric secretions, regurgitation of gastric secretions into the esophagus and mouth causing burning in the epigastric region and behind the sternum, persistent dryness of the throat and tongue which is frequently fissured. The pain and regurgitation are aggravated when the patient lies on his back, so that he seeks a comfortable position for relief of these symptoms. In most of these instances the cancer is a slowly growing scirrhus type and the roentgenological evidence reveals a rigid pars media, absence of peristalsis, and occasionally actual deformity of the pars media.

A rarer site of cancer of the stomach is the cardia. Deglutition disturbance is the earliest symptom, and cardiospasm is always present. It may be extremely difficult at times to detect the cancer roentgenologically.

No effort should be spared in this direction. Films should be taken in every possible position, namely, standing, recumbent, supine, right and left oblique and particularly in the Levy-Dorn position, i e, with the patient in the supine position, buttocks elevated, the rays directed to the cardiac end. It is of great importance that every effort should be made to visualize the air bubble. Deformity of the air bubble is an important sign in cancer of that location. If the air bubble is not visualized, it is advisable to give the patient a Seidlitz



FIG 4 Annular carcinoma of pylorus showing obstruction

powder, and within two to five minutes, to take another roentgenogram. This often facilitates the roentgenological visualization of the air bubble. If the aspirated contents by stomach tube show an excess of blood, particularly old blood, it is of diagnostic importance. Esophagoscopy and gastroscopy are of diagnostic aid. Recent surgical advances for cancer in this region¹⁴ have facilitated more satisfactory treatment of this type of lesion than in the past and may extend the opportunity for favorable life expectancy. We know from experience that many of these cases are looked upon as nervous cardiospasm. During the time that elapses without any interven-

tion, avitaminosis and dehydration usually result, so that the poor condition of the patient renders surgery impossible

Another site for a slowly developing carcinoma is the entire posterior wall of the stomach without invasion of the anterior wall or curvatures, in which the roentgenogram is negative and no mass is palpable. Only gastroscopic examination with a biopsy can establish the diagnosis. Pain in the upper abdomen independent of meals is the most striking symptom, but the diagnosis may be overlooked for months or even years because of the negative findings. Early gastroscopic examination in these cases is, therefore, urgent.

Scirrhus carcinoma of the entire stomach, or a "leather bottle stomach" roentgenologically, the stomach appearing as a narrow, rigid tube, is another rare and slowly growing malignancy. The stomach is transversely placed, well above the umbilicus. Fluoroscopically, the barium is seen to pass through so rapidly that within a half or three-quarters of an hour, the entire stomach is empty. The air bubble is very small or entirely absent. The fundus is either absent or very small. Often the barium is regurgitated into the esophagus, and the esophagus and stomach appear as two tubes (figure 5)—a vertical (esophagus) connecting with a transverse (stomach) tube. The lesion is frequently called linitis plastica. Because of its slowness of growth, it acts almost like a benign lesion, yet its eventual outcome is that of any slowly growing carcinoma. These cases have complete absence of HCl and ferments (achylia).

We have dwelt in detail on the slowly growing types of cancer that develop on a healthy gastric mucous membrane. They should be subjected to surgery even if a large palpable mass is present because there is no tendency to early metastasis. Although radical surgery is necessary, with a mortality as high as 10 to 15 per cent, if the operation is successful, lasting and good results may be expected. Without operative intervention it must be remembered that the mortality is 100 per cent.

It is very difficult to foretell the percentage of five year survivals or even cures in the above groups of cases, but it may be said that in the absence of metastases, and with a successful operation, the patient can go on for many years without recurrence. In these cases the presence of a marked secondary anemia should not deter one from surgical intervention provided there is adequate preoperative preparation. When there has been prolonged obstruction and marked atony of the stomach one should resort to gastric lavage for 10 to 12 days preceding operation. If the patient is very weak, it may be advisable to do a two stage operation, i.e. gastroenterostomy followed by a resection about one month later.

The medullary form of carcinoma of the stomach usually arises on a previously healthy mucous membrane, grows very rapidly and has a tendency to early metastases. The metastases are through the lymphatics, mainly to the neighboring glands, and to the liver, but may also spread quickly to the peritoneum and to the pouch of Douglas. In rare instances metastases may

spread by way of the blood to distant organs In the early stage the growth in the liver consists of numerous small nodules There is usually anemia

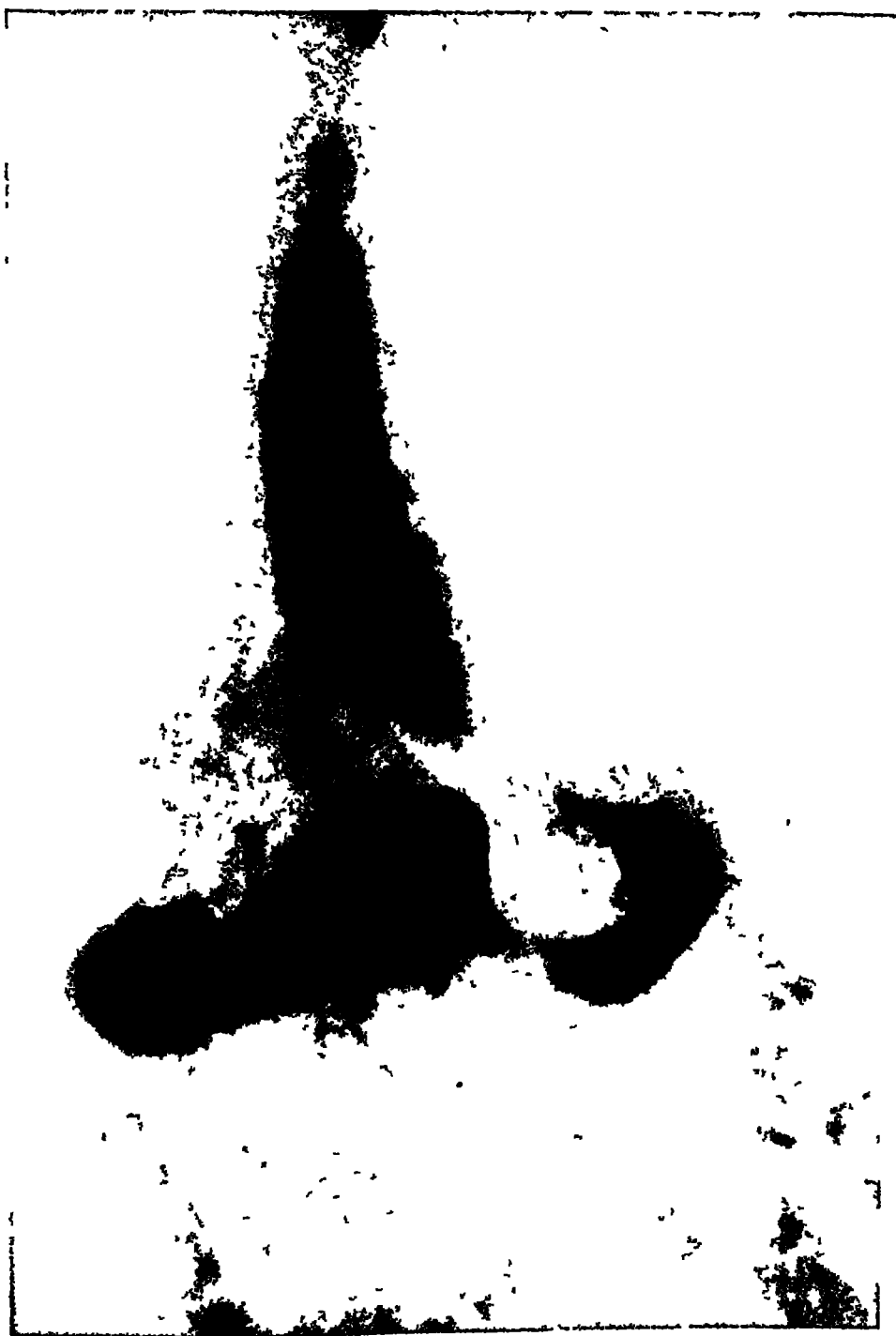


FIG. 5 Scirrhus carcinoma of entire stomach, where esophagus and stomach appear as two tubes at right angles to each other

varying in degree The symptoms are gastric distress, rapid loss of appetite, loss of weight, occasional epigastric pain and early evidence of cachexia A palpable mass can be detected early in the epigastric region Roentgen-ray

shows an eaten out pars media, extending to the pylorus (figure 6) If the liver is not very large and nodular, if there is no ascites and there is no rectal shelf, and jaundice is absent, it is advisable to prepare the patient carefully by blood transfusion for surgical intervention It is well known that most surgeons, finding only a few nodules in the liver, may do a gastrectomy with removal of some of the glands If the patient survives the operation, he may be comfortable for a year or even longer However, the immediate



FIG 6 Medullary carcinoma (Stomach photographed from left to right)

mortality may be as high as 30 to 40 per cent We agree with A A Berg (personal communication) that the above cases are just as much entitled to prolongation of life and a comfortable existence as those patients whom the internist treats for renal disease with progressive uremia, or progressive heart failure, although the span of life will not be long

Finally, there are cases, fortunately smaller in number, in which the metastases are mainly through the blood stream and partially through the lymphatics The primary gastric growth is usually very small, at times no larger than a hazel nut The local gastric symptoms are insignificant The

patient may present himself with complaints of weakness, elevation of temperature, increased respirations. The physical signs in the lungs may be very meager, but the roentgen-ray examination of the chest shows evidence of lymphangitis carcinomatosa. In rare instances, metastases may be present in the brain, so that the symptoms may lead to an erroneous diagnosis of primary brain tumor. These cases, because of their widespread metastases, are not amenable to surgical intervention.

Of major importance in this discussion are the remaining 30 per cent of the cases in which the cancerous lesion develops on a previously diseased mucous membrane. This group comprises patients who have had gastric complaints for many years before cancer developed, and those in whom the growth of cancer is so slow, as shown by Eusterman² and others, that the lesion remains localized for several years.

The precancerous symptoms vary in nature and are usually very bizarre and noncharacteristic, and are, therefore, interpreted mostly as neurogenic. There are three separate groups of clinical entities on the soil of which the cancer develops: (1) gastritis, (2) polyps, and (3) gastric ulcers.

Gastritis. The most important group comprises cases of gastritis. The appreciation and absolute clinical establishment of this condition must be credited to the significant work of Schindler³ and his co-workers. Schindler perfected the flexible gastroscope and was able to demonstrate that gastritis is by no means rare, and he showed that on the basis of gastritis cancer may develop in some instances. His contribution is of extreme importance in that it made observers conscious that many cases which were interpreted as having functional disorders were in reality suffering from gastritis. Schindler furthermore called attention to the fact that if the symptoms become aggravated and the patient showed evidence of wasting, the gastroscope may establish the presence of early cancer before roentgen diagnosis is possible, thus enabling early surgical intervention and possibility of permanent cure.

In order to establish the diagnosis of primary gastritis we must evaluate its accompanying symptoms, especially since they are not characteristic. The patient usually has a very sensitive digestive apparatus, a capricious appetite, a coated tongue, a dry mouth, and pain is conspicuously absent. Upper abdominal distress which may persist for days or weeks is a very frequent symptom. Because of the chronicity of the condition, the patient becomes accustomed to the symptoms with the result that the loss of weight may be offset by a sufficient qualitative food intake. If there be an accidental error in diet, recurrence of symptoms usually results. The patient is constipated and persistent pyrosis may be present not only in the epigastrium but often behind the sternum. There is regurgitation of food or gastric secretion of disagreeable taste, and sometimes of an offensive odor. In most cases, the gastric secretions are qualitatively and even quantitatively affected. Subacidity is the rule, provoking the question as to whether there is diminution of actual secretion, or whether the normal gastric secretion is neu-

tralized by the excessive gastric mucus due to the presence of catarrh. In the vast majority of cases the latter condition exists, and is demonstrable by the aspirated gastric contents. Macroscopically there is a large quantity of mucus, microscopically, there are red and white cells in addition to mucous shreds.

Roentgen-ray studies of the mucous membrane show definite thickening of the gastric rugae and deposits of islands of barium varying in size and shape.

Patients with gastritis as a rule are not awakened by pain, as is the case in gall-bladder disease or peptic ulcer. In persistent true achylia there may be a tendency to loose bowel movements (gastrogenic diarrhea) and also poor digestion of meat, the latter explaining the presence of undigested meat fibers in the stools.

Schindler has stressed the fact that in all forms of gastritis, extragastric symptoms such as headache, nervousness, numbness and tingling of the fingers and toes may be present.

If such patients begin to show persistent and aggravated gastric digestive disturbances, they must be observed at regular intervals of three months, both gastroscopic and roentgenologic studies, in order to detect the presence of malignancy as early as possible. Both these studies are essential. Even in the hands of the most skillful gastroscopist, one will encounter an occasional case in which the presence of a small carcinoma may escape detection. Roentgenologic evidence of stiffening of the pars media and pylorus or very active or complete absence of peristalsis of the pars media and pylorus, justifies surgical exploration. Schindler and many others state that it is very difficult to detect a small lesion high up in the fundus, gastroscopically, contrary to what one would expect. Early evidence of incomplete cardiospasm and deformity of the air bag, imperfect visualization of the cardiac end of the stomach and slight deformity of the same when films are taken in varying positions (as described above) may lead to earlier suspicion and even a diagnosis by roentgenogram. On the other hand, when a lesion is situated on the posterior wall of the pars media, especially if it is the slowly growing, flat carcinoma of the scirrhous type, only by use of the gastroscope can positive evidence in this early state be demonstrated. Roentgenologically, even considerable involvement of the posterior wall may escape detection.

Of vital importance from the practical point of view is cancer of the pyloric portion. Here both gastroscopic and roentgen examinations may at first be disappointing, but occasionally, at an early stage, although the pylorus may be regular in outline, it is narrower than normal, resembling pylorospasm. A narrowed pylorus in conjunction with anacidity is very suspicious of cancer. However, pylorospasm secondary to gall-bladder disease may also exist, as first pointed out by Holzkecht and Luger.⁴ If pylorospasm persists, even though gastroscopic examination is negative, exploratory laparotomy is justifiable.

Polyps There are two types of polyps, namely, the congenital and the acquired

The congenital type may be single or multiple and pedunculated. The multiple congenital polyps are usually small. The single type may reach a large size. We have encountered a case in which the polyp was the size of a tangerine. These polyps are usually asymptomatic and are only accidentally discovered, either at postmortem examination, or roentgenologically by the appearance of negative circular shadows in the stomach. At times they bleed, and the large single polyp may give rise to uncontrollable hemorrhage which can be stopped only by operative intervention.

Of greater importance from the standpoint of the development of cancer is the acquired type of polyp. This originates on the basis of gastritis (gastritis polyposa). Gastroscopy and biopsy are the conclusive diagnostic methods and surgery is indicated if the findings warrant it.

Gastric Ulcer Finally, we have the third group, gastric cancer on an ulcer basis. There is still a great deal of controversy and extreme divergence of opinion as to the frequency with which gastric ulcer eventually becomes malignant. The painstaking studies of Wilson and McCarty⁵ of the Mayo Clinic on this subject were originally quoted as indicating between 60 and 70 per cent. The erroneous impression was created that in 60 or 70 per cent of ulcers a cancer developed. What they actually meant was that in 60 or 70 per cent of cancer cases there was a previous ulcer. They paid strict attention to the cytology of the lesion. If elongated and deformed cells (cytoplasia) were found in the base of the ulcer, it was considered malignant. Finsterer, who in great measure agrees with these observations, is of the opinion that the cytoplasia must involve the edges of the ulcer as well. Some pathologists, particularly keen observers like Aschoff⁶ and Ewing,⁷ do not share this opinion. The former states that the highest percentage he encountered on an ulcer basis was 2½ to 3 per cent, and furthermore, that, "cancer can frequently ulcerate, but an ulcer seldom cancerates." Ewing doubts completely the existence of cancer on an ulcer basis. Schindler is uncompromising in his opinion. He denies completely the occurrence of cancer on an ulcer basis.

It has been our experience with cases in which the history could be traced, that gastric ulcer has preceded the onset of cancer by a number of years. We stated in a previous communication⁸ that it may occur in 2 to 3 per cent of the cases. It is rather striking that in a recent contribution, Walters⁹ stated that in one-third of the cases operated on for cancer of the stomach, there had been ulcer symptoms. We have similarly encountered cases of proved clinical cancer, in which the symptoms were those of ulcer, although no ulcer ever existed.

In this group there are two subgroups, one in which ulcer actually preceded the development of cancer, and the second in which the cancer begins with ulcer symptoms, without the presence of ulcer. We wish to stress the fact that in both subgroups the symptoms of cancer develop gradually, the

lesion is more benign in its behavior and, therefore, more likely to be resectable, and the opportunities for prolonged or even permanent cures are more favorable. It is evident that we must analyze the symptoms and signs of such cases with great care.

In the first group, the subjective symptoms of peptic ulcer have existed for a great number of years. There is also definite evidence of ulcer roentgenologically, either in the form of a niche in the pars media or definite evidence of ulcer in the prepyloric area. These lesions may periodically appear or disappear, with corresponding changes in subjective symptoms. In those cases in which there is reason to suspect a change to malignancy, the subjective symptoms persist and are somewhat altered in character. Instead of pure hunger pain, there is a persistent gnawing pain in the epigastrium radiating to the spine. Even during the pain free intervals there is a persistent sensation of bloatedness. During the night the patient is distressed by distention and actual pain, and only slightly relieved by alkalis, or not at all. Milk, which always gave relief in the past, now gives distress. Pyrosis is persistent and extends into the esophagus. Appetite becomes markedly diminished. The tongue becomes coated. Loss of weight is out of proportion to the diminished food intake. Weakness and gradual anemia ensue. Anemia is invariably hypochromic and is due in the majority of cases to inanition and avitaminosis and in many instances is a result of persistent occult bleeding which is demonstrable in the stool or stomach contents. The physical examination may be entirely negative except for persistent tenderness in the pyloric or epigastric region. Examination of the gastric contents will show a tendency to subacidity. Examination of the fasting gastric secretion will invariably show microscopic and even macroscopic retention of food eaten the night before. This retention may be best studied by giving the patient eight or 10 raisins, currants, or a few plums the night before. We emphasize the importance of microscopic and macroscopic retention as an early sign of gastric motility disturbance in these cases at a time when the barium meal shows no disturbance in motility.

What are the roentgenological signs indicative of transformation of a benign ulcer to malignancy? Carman¹⁰ expressed his view that an ulcer on the lesser curvature of the stomach with a niche having a diameter 2.5 cm. or more should be regarded as malignant and should be submitted to surgery. In his later studies, based on a great deal of experience roentgenologically and with postoperative specimens, he stated that ulcer niches that become malignant have special features, namely, they appear meniscus-shaped with the convexity towards the gastric wall and the concavity towards the lumen when viewed in profile. However, we have encountered cases in which the niche fulfilled the requirements for the diagnosis of malignancy as set down by Carman, yet the patient made a complete recovery after weeks of treatment and continued well for many years.

Even before Carman described the size and meniscus niche as indicating carcinomatous degeneration of ulcer, two cases in our experience are worthy

of mention The first was a male, about 43 years old, who had ulcer symptoms for many years There was a niche on the lesser curvature 4 to 5 cm in diameter, with considerable deformity of the pars media At operation, Dr Leo Buerger found that owing to the fact that the posterior wall was adherent to the pancreas, resection of the ulcer (the procedure of choice in those days) and even posterior gastroenterostomy were impossible Therefore, an anterior gastroenterostomy was done After a stormy convalescence the patient recovered and remained symptom-free for at least 15 years when he was lost sight of The second case was that of a male in his late forties, showing roentgen evidence of a niche about 3 cm in diameter with considerable indentation of the greater curvature He was operated on by Dr J F Erdmann A local excision with posterior gastroenterostomy was done Pathological report was ulcer, benign The patient had many years of comfort postoperatively

Since that time we have seen, and other observers have reported, numerous cases with niches varying from 6 to 10 cm in which thorough pathological studies failed to reveal any evidence of malignancy

Many of these ulcers of more than 2.5 cm may heal after medical treatment However, there may be recurrences, but this is still not sufficient evidence that the ulcer is cancerous It must be emphasized that when there is a niche particularly on the lesser curvature, because of the excavation of an ulcer area and weakening of the adjacent wall, increased intragastric pressure by the filled stomach will cause a ballooning out of this area with protrusion In such instances, on one examination the effect of intragastric pressure causes the niche to appear on roentgenogram When the stomach is only partially filled some hours later, the niche has disappeared Within a short time, when the ulcer is in the process of healing, the increased intragastric pressure no longer produces the niche effect This explains why many cases are reported in which a niche has disappeared rapidly, and within a week or two the patient has a gastric hemorrhage

On the other hand, there is another form of niche due to an ulcer on the lesser curvature which penetrates beyond the wall and becomes adherent to surrounding structures In these cases, between the wall of the stomach and the niche there is a vacant space The niche itself is often triangular rather than circular Occasionally an air bubble may be seen on top of the niche A niche of this type will be smaller when healing takes place, but some evidence of the niche remains even though the patient is symptom free Held and Gray¹¹ suggested that the term *diverticulum* was more descriptive than the term niche They spoke of two types one that did not penetrate beyond the wall of the stomach was termed "pulsion diverticulum," and the penetrating type with adhesions to the surrounding structures was called "pulsion-traction diverticulum" Rehfuss¹² is in concurrence with this concept

Conversely, a small sized niche less than 2.5 cm, on the basis of ulcer, may be the site of cancer formation This has been recently reemphasized

by Eusterman¹⁸ We recall a 43 year old male, with only a three to four year history of ulcer symptoms, who because of frequent recurrence of symptoms and inability to carry out medical treatment, asked for operative intervention. An ulcer of very small size on the lesser curvature was excised. The pathologist reported benign ulcer. The patient felt well for one and a half years, then began to suffer a recurrence of symptoms, presenting himself with an immense palpable mass in the epigastrium and a large liver. He was again operated on, and an inoperable carcinoma was found. In retrospect, we now feel that at the time of the first operation, there were already some cancerous changes in the ulcer which were not correctly evaluated by the pathologist, or that the early niche was primarily due to cancer.

What should be the criteria in determining whether an ulcer has become cancerous? It seems to us that the most stress should be placed on the greater persistence and aggravation of symptoms. Pain becomes worse and is not relieved by the intake of food, appetite diminishes, and there is gradual loss of weight. In these cases, above all, gastroscopy with biopsy must be done.

In the prepyloric region, if an ulcer becomes cancerous, we must rely on the clinical and gastroscopic evidence. Roentgen-ray examination may be extremely disappointing. If the patient has been previously examined by roentgen-rays, and some time later shows irregularity of the pylorus and progressive delay in the emptying, we have reason enough to resort to exploratory laparotomy. Clinically, vomiting is present despite the fact that stenosis is not complete. Fluoroscopic examination may show marked diminution in the peristalsis in the pyloric region and compensatory hyperperistalsis in the pars media. There is never the characteristic atony of benign stenosis. In the presence of the above findings, despite negative gastroscopic examination, surgical intervention is absolutely indicated.

The following case is cited here because it illustrates two important points: first, that carcinoma of the stomach can occur on an ulcer basis, second, that such a cancer, when resected, can give lasting local results without any local recurrence. The case is that of a male in the mid-fifties, who had suffered periodically from ulcer symptoms for 25 years. He suddenly began to have persistent pain and moderate loss of weight, but no definite roentgenologic evidence of cancer was demonstrable, except for slight deformity of the pylorus. No mass was palpable. He was operated on by Dr. Leon Ginzburg (at the Mount Sinai Hospital), who did a resection for pyloric cancer. The patient made an uneventful recovery, and felt perfectly well for about two years, when he again developed abdominal symptoms. This time a palpable mass in the mid-abdomen was felt. It was looked upon as a recurrence. Dr. Ginzburg* reoperated and found the cancer in the transverse colon. Dr. Paul Klemperer, pathologist at Mount Sinai, re-

* This was reported to us by Dr. Ginzburg, with whose consent we mention it here, since we did not see the patient at the time of recurrence of symptoms.

ported that the growth was an independent cancer, completely unrelated to the cancer previously found in the stomach. The cancer of the transverse colon was resected, and the patient again made an uneventful recovery.

There is a large group of cases in which the patient has ulcer symptoms, the underlying lesion, however, starting as cancer. Such cases simulate ulcer in that they have hunger pains and are relieved by the intake of food. However, there is a lack of periodicity, and unlike ulcer in which psychic trauma aggravates the symptoms, here dietetic errors play the major rôle. These errors lead to an increasing exclusion of many articles of food. The patient attributes the loss of weight to lack of food, but the loss of weight is even out of proportion to the diminished food intake. Sooner or later the appetite becomes capricious. These patients usually develop symptoms in the late forties or fifties. In most of them the roentgenologic examination may be entirely negative. Even careful mucous membrane studies may be uninformative. In order not to overlook the lesion, frequent gastroscopic examinations should be made, and even a suspicious finding is sufficient indication for operation. It is in these cases that valuable time may be lost in waiting for palpable or roentgenologic evidence.

Anemia Since many of the cases of gastric cancer are accompanied by a marked anemia it would be well to analyze the anemia more carefully. Two types occur, a hyperchromic and a hypochromic anemia. It is very important to differentiate between these two clinically, because the therapy to combat each type is different.

The hyperchromic type of anemia co-existing with achylia in a case of carcinoma simulates the picture of pernicious anemia. The diagnosis of carcinoma having been established, it is necessary to introduce liver therapy besides blood transfusions and iron.

The hypochromic type of anemia should respond to blood transfusions and iron. In rare instances, the presence of a high degree of anemia may lead one to suspect actual bone marrow involvement due to metastases. Although bone metastases in cancer of the stomach are uncommon, some observers have reported an incidence as high as 5 per cent. All efforts should be made to diagnose the presence of bone metastases. Increased blood phosphatase and prolonged sedimentation time are sometimes found with bone metastases. Roentgen examination, particularly of the pelvis, spine and skull, should be done.

Farrow and Woodward have suggested that these patients should have four to five injections of testosterone propionate; if the concentration of calcium in the serum and its excretion in the urine are markedly increased bone metastasis should be suspected. In two cases, similar changes followed injections of estrone.

Finally, the study of bone marrow for the presence of cancer cells should not be neglected.

CONCLUSION

1 Despite all efforts at early diagnosis of cancer of the stomach, a large percentage of such cases are inoperable because of the extreme malignancy and rapid metastases

2 Some cases are inoperable because the lesion exists in a silent area of the stomach and is asymptomatic until advanced beyond operability

3 The percentage of cases (30 to 40 per cent) in which operability and even permanent cure is possible is of great practical importance. In these cases early diagnosis is most essential. Recent experiences have shown that gastroscopic examination has materially increased the percentage of early diagnosis of cancer.

4 We must bear in mind that cases of cancer which develop on a previously diseased mucous membrane as in case of gastritis, polyposis, gastric ulcer, have a tendency to grow much slower, are more benign in character and when diagnosed early, offer the patient a great chance for prolongation of life and even permanent cure.

5 Individuals with ulcer symptoms, without ulcer signs, should be looked upon with greater suspicion and more watchfulness for early cancer than those in whom ulcer is clinically and roentgenologically demonstrable.

6 The high degree of anemia and the size of the palpable mass should not deter one from operative intervention provided preoperative and post-operative treatment are carried out with the greatest care.

BIBLIOGRAPHY^{*}

- 1 HOLZKNECHT, G. Die Röntgendiagnostik des Magens, Jahreskurse f. ärztl. Fortb., August 1911, p. 88.
- 2 EUSTERMANN, G. B. Gastric carcinoma masquerading as benign ulcer, Libman Anniversary Volumes, 1932, 1, 385.
- 3 SCHINDLER, R. Gastroscopy: the endoscopic study of gastric pathology, 1937, Univ. of Chicago Press, Chicago.
- 4 HOLZKNECHT, G., and LUGER, A. Zur Pathologie und Diagnostik des Gastrosplasms, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxi, 669-694.
- 5 WILSON, L. B., and McCARTY, W. C. The pathological relationships of gastric ulcer and gastric carcinoma, Am. Jr. Med. Sci., 1909, cxliii, 846-852.
- 6 ASCHOFF, L. Deutsch. med. Wchnschr., 1912, xxxviii, 494.
- 7 EWING, J. Relation of gastric ulcer to cancer, Ann. Surg., 1918, lvi, 715.
- 8 HELD, I. W., and GOLDBLOOM, A. A. Carcinomatous degeneration of peptic ulcer, Surg. Clin. N. Am., 1933, viii, 387-401.
- 9 WALTERS, W., GRAY, H. K., and PRIESTLY, J. T. Malignant lesions of the stomach: importance of early treatment and end results, Jr. Am. Med. Assoc., 1941, cxvii, 1675.
- 10 CARMAN, RUSSEL D. Roentgen diagnosis of diseases of the alimentary canal 1920, W. B. Saunders & Co., Philadelphia.
- 11 HELD, I. W., and GRAY, I. Present status of roentgen diagnosis of gastric and duodenal ulcer, Med. Clin. N. Am., 1925, ix, 755-808.
- 12 REHFUSS, M. E. Diagnosis and treatment of diseases of the stomach 1927, W. B. Saunders Co., Philadelphia.
- 13 EUSTERMANN, G. B. Carcinomatous ulcer, Jr. Am. Med. Assoc., 1942, cxviii, 1.
- 14 GARLOCK, J. H. The problem of carcinoma of the cardiac end of the stomach. S. G., Gynec. and Obst., 1941, lxxiii, 244.

THE LEAVEN OF PSYCHOSOMATIC MEDICINE *

By EDWARD A. STRECKER, M D , F A C P , *Philadelphia, Pennsylvania*

THE accomplishments of psychosomatic medicine are noteworthy, its objective is magnificent, but the name is unfortunate. Its comparatively recent usage makes it sound like the announcement of a marriage between body and mind, with the subdivisions and specialties of medicine and psychiatry in the bridal party. If the union of body and mind has just been consummated, then psychiatry for some time has sanctioned an illicit relationship. Long before the word psychosomatic was compounded, psychiatry had insistently taught that man was a total and indivisible unit and, therefore, in health and disease, every somatic process at once reverberated in all of the man and notably in his emotions, conversely that every emotional reaction, whether it was violent and pathological, like rage, or merely a feeling tone, like a mild state of satisfaction, immediately had repercussions in every tissue and cell of the body.

The basic idea of psychosomatic medicine is very ancient. More than 2500 years ago, the wise Socrates, returning from the Thracian campaign, reported that the Thracians realized that the body could not be cured without the mind. "This," he said, "is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole."

Nor was the appreciation of the entwining of the body and mind confined to the elect. From time immemorial it has been reflected in the language of the people. "I felt a lump in my throat", "My heart jumped", "My stomach dropped", "I felt as though I had been pulled through a wringer", etc.

Our allies, the Chinese, no doubt stimulated by frequent food scarcities, have elevated the stomach to a sentimental plane. Two lovers separated from each other might write in this vein. "My stomach is hungry for you." So, too, is there a psychosomatic note in this ancient and beautiful Chinese wish. "May Joy sing in the topmost boughs of your heart."

The dough of psychosomatic medicine was ready for a long time, but it needed the yeast of concrete evidence. This was supplied by the focusing of attention upon a group of clinical situations in which functional and structural met; or more accurately, a long path of functional symptoms, perhaps gastrointestinal, due to the anxiety of emotional conflict, came to the end of the trail in the structural pathology of a peptic ulcer. The yeast now became activated and the leavening began.

Evidence was offered from every department of medicine and its specialties. One treatise alone listed 2251 references in this order of observed

* Presented at the meeting of the American College of Physicians, St. Paul, Minnesota, April 20, 1942.

frequency cardiovascular, genitourinary, gastrointestinal, general metabolism, endocrine, respiratory, dermatological, special senses, nervous system, musculature, osseous system

In internal medicine and its various divisions how effective in terms of treatment will be the psychosomatic leavening? Presumably internists, cardiologists, genitourinary specialists, gastroenterologists, endocrinologists, dermatologists, laryngologists and others will continue to treat patients whose functional symptoms fall into the groups in the treatment of which they are skilled. This is right and proper. Those specialists who understand the real implications of "functional" will continue to treat patients successfully. However, there are others who are not so well informed.

The gastroenterologist, the genitourinary specialist, the dermatologist and others have aimentaria, instrumental and pharmacological, useful in the treatment not only of organic but of functional symptoms. There is nothing in the determinations of psychosomatic medicine which would frown upon the employment of specialized technics and drugs. Even psychiatrists prescribe drugs, massage, hydrotherapy, heliotherapy and many other measures. Functional symptoms involve the revolution of a vicious somatopsychic circle—emotional, functional derangements of organs expressive of the emotional conflict, more emotional reaction, more functional incapacity and so on, until the human machine runs down or, perhaps, gives out, and there remains the scar of structural pathology. Often, it is legitimate to attempt to interrupt the revolution of the vicious circle in any of its segments and sometimes well conceived and directed physical and drug therapies are followed by considerable improvement.

There are certain conditions under which concrete therapies are not helpful, and indeed are harmful, serving only to impress more deeply the functional symptoms which are present or others which may take their place.

These conditions are as follows

- 1 If the patient is not given clearly to understand that these various special therapies and drugs, although they may be symptomatically helpful, may lessen somatic distress and promote general improvement, yet of themselves cannot bring about adjustment or recovery

- 2 This situation becomes particularly dangerous if the patient comes to believe that the symptoms are actually due to some insignificant or conjectural defect—a minor deviation, a dead tooth, a trifling ptosis of the stomach. Once patients believe these things firmly, then the impress of the functional symptom-complex becomes indelible and hope of recovery passes.

- 3 The most important condition is the failure to recognize underlying fundamental psychopathology and to utilize the understanding acquired in the basic treatment of the functional symptoms. If this is not done, it is as grievous an error as would be the failure to remove a beginning malignancy of the breast. Failure to do this could not be compensated for by any amount of expert care, vitamin therapy and special treatments. Neither

can any amount of instrumentation, gall-bladder drainages, vaccines, endocrine therapy, etc., bring about a favorable result unless the determining underlying emotional conflict is resolved

Perhaps, these three actual and very usual situations will be illustrative

CASE REPORTS

Case 1 A man 49 years old, with a wife 35 and two healthy children, described himself as desperate because he was sexually impotent. Pathetically he told of treatments to regain potency and happiness: genitourinary instrumentation, general and prostatic massage, hydrotherapy, electrotherapy, heliotherapy, a sheaf of prescriptions for endocrine products, faithfully taken. His impotence was no better. Indeed, to it had been added annoying sensations and sharp pains in the perineum, burning on urination, nocturnal emissions, headaches, insomnia, loss of energy and concentration, etc.

Case 2 A married woman, aged 42, complained of severe nausea, "sick stomach," vomiting, anorexia, headache, backache, vertigo, etc. She had had two rest cures, numerous gastrointestinal roentgenograms, special corsets for gastroptosis, and now she was having weekly gall-bladder drainages.

Case 3 A 22-year-old student wanted to leave college since he felt he was too sick to go on and as he said "I would rather quit than flunk. It's no use trying. I can't concentrate."

Tuberculosis had been suspected. He was being given nose and throat treatments twice weekly. He had had many dietary and rest treatments, efforts to increase his weight.

At the very first interview in each instance, the following facts were elicited. They had never been brought to the surface before.

Case 1 The man with the impotence had been dominated far into manhood by a positive, aggressive mother. He was 14 years older than his wife whose sex needs were strong. His symptoms appeared after an unsuccessful attempt at sexual intercourse. He thought his wife was irritated and impatient at his failure.

Case 2 The woman with the gastrointestinal symptoms had lost sexual desire. Sexual relations had become unpleasant and painful. By various subterfuges she had decreased the frequency of the sex act, but was filled with anxiety, lest her husband should tire of her and leave her.

Case 3 The young student was enormously relieved at being given the opportunity of relieving his mind, deeply troubled and remorseful, because of masturbation. During much of his life he had been tied too tightly to the apron strings of an emotionally possessive mother. She had warned him excessively about "girls." The masturbation had not been continuous from childhood but had been resumed soon after entering college, upon the heels of three heterosexual experiences, occurring in a setting conducive to embarrassment, feelings of inferiority and fear of discovery.

Three clinical situations have been briefly and crudely sketched. On the one hand, there were genitourinary examinations, gastrointestinal and gall-bladder tests, studies of the nose, throat and sinuses, and roentgenograms of the chest, on the other hand, a surface revealing of three emotional conflicts. The first, the physical, dictated a variety of physical therapy, urethral instrumentation, prostatic massage, general massage, hydrotherapy, endocrine medication, the wearing of special corsets, gall-bladder drainage,

nose and throat treatments, rests and diets, the second, the emotional, led to a moderate amount of psychotherapy, to the opportunity to talk over troubles that were not physical, to explanation of underlying mechanisms and a frank facing of their implications, to correction of faulty mental attitudes, and to slight adjustments in the environment

If the obvious lessons which these clinical situations and thousands of similar ones teach are not learned and learned well by all of us, then the yeast of psychosomatic medicine will fail to leaven the dough of practice, and there will be only a half-baked loaf which would fall far short of rising to the promised and anticipated level of medical progress

Under the protection of my brother Fellows of the American College of Physicians, I am emboldened to hint that surgeons might well profit from the lessons of psychosomatic medicine. The scalpel of the surgeon, no matter how skillfully wielded, often cannot avoid cutting through protective psychological tissues. By this, I mean that every human being has one and usually more flaws in his or her psychological armor. However, the majority of us meet life adequately enough in spite of our flaws. Nevertheless if, when the psychological resistance is lowered, an opportunity presents, then the flaw will be enlarged, the area of vulnerability increased and functional protective symptoms will appear as an escape mechanism. Often a surgical operation is such an opportunity. Whenever possible, there should be a psychological survey before an operation, adequate psychological preparation for anesthesia and postoperative treatment which is not only surgical but also psychological. Attention to these few measures based on the principles of psychosomatic medicine would prevent a deal of chronic functional invalidism.

The way to get something done thoroughly is to begin at the beginning. The beginning is in the preclinical years of medical education. Medicine not only has its physics or somatics but also its "psychics" or psychogenetics. There could be a true and helpful teaching parallel. If there are livers and spleens and hearts in anatomy, so, too, is there an anatomy of psychology which should study normal emotions, consciousness, memory, etc. If there is a physiology which teaches how organs work, so too, and at the same time, should a physiology of mental functions be taught. The student should learn how they work. Paralleling histology, the microscopic study of normal organs and tissues, there should be given opportunities to become familiar with the finer subdivisions of mental functions, for instance, remote and recent memory, the gradations of normal consciousness, the infinite variety of emotional shadings. When the Department of Pathology is demonstrating gross morbid lesions, luetic aortitis, liver abscess and what not, the Department of Psychiatry should be showing the gross pathology of the mind, marked emotional deviations like profound melancholia or complete dementia. Likewise should there be the twin teaching of microscopic pathology, let us say, on the one hand, the study of a cross-section of an arteriosclerotic vessel or the walls of an abscess, on the other a span of

amnesia or the degrees of katatonic stupor. If the loaf of medical practice is to be thoroughly leavened, the medical student must be given from his first week in medical school the opportunity of studying all of the man and not only a hypothetical somatic half.

We are in the midst of the greatest World War that has ever cursed humanity. As it happens, among other things modern war constitutes a huge laboratory of psychosomatic medicine. Statistics from World War No. 1 indicate that one-seventh of all war casualties were neuropsychiatric and, excluding wounds, the proportion was one-third. The Veterans' Bureau has already expended more than one billion dollars for the care of neuropsychiatric disabilities incurred in World War No. 1. I think I may predict with safety that the neuropsychiatric problem eventuating from this war will be much greater than from the previous one.

As you know, these casualties will be largely psychoneurotic. They will consist of "shell shock" (conversion hysteria), neurasthenia, anxiety neuroses, and a relatively smaller number of psychoses. In other words, a very large majority of the casualties will consist of functional symptoms, that is, there will be demonstrated again on a massive scale the close entwining of body and mind and there will be clinical examples that properly fall within the domain of psychosomatic medicine.

Reports would already indicate that a very large number of functional symptoms are within the gastrointestinal field. Furthermore, there have been definite indications that sometimes anxiety is productive of structural pathology, perhaps chiefly peptic ulcer.

It is important to note that there has been a definite difference in the Army and in civilian life. I think there will be no change in the number of neuropsychiatric casualties in the armed forces. As a result of bombing in England, in London, Liverpool, Coventry, Plymouth and other places, it appears that functional symptoms in civilians are quite rare and constitute less than 2 per cent of the hospital admissions. Here we have an important fact which needs thorough consideration by the students of psychosomatic medicine. Evidently, even though the stress and strain are great, if the human being is not away from his home and from those whom he loves and who love him, he does not succumb to "shell shock." This means that he retains a protective measure of security.

In closing, may I say that in this great war crisis which is being fought on so many fronts we need another Socrates. Indeed, we need more than one. If we can have them, I predict that they will return after the war is over and tell us in much the same words that Socrates told the Greeks after he returned from the second Thracian campaign: "It is important, extremely important, never to forget the close relationship between the body and the emotions and it is important to remember that the body cannot be cured without close attention to the mind."

SEVERE INJURY TO KIDNEYS AND BRAIN FOLLOWING SULFATHIAZOLE ADMINISTRATION: HIGH SERUM SODIUM AND CHLORIDE LEVELS AND PERSISTENT CEREBRAL DAMAGE *

By JOHN A. LUETSCHER, JR., and SAM S. BLACKMAN, JR.,
Baltimore, Maryland

FIVE patients with a history of recent sulfonamide medication have developed an unusual type of renal insufficiency, as well as evidence of injury to the brain. The patients presented a temporary, severe disturbance of serum sodium and chloride concentration, which was responsible, at least in part, for the death of two patients. In all cases there were signs of injury to the central nervous system, which persisted in two patients despite return of the blood chemistry to normal.

Case 1 This 25 year old colored laborer was brought to the hospital because of vomiting and delirium. His past health had been good. Ten days before admission he complained of fever, cough, and pain in the chest. Three days later his physician found signs of pneumonia and prescribed sulfathiazole, 3 grams per day for two days and then 15 grams per day for four more days. On the second day of treatment, the patient began to vomit. After three days of sulfathiazole therapy, he retained no food or fluids and passed little or no urine. He became drowsy, confused, and finally delirious.

On admission to the hospital, a week after the first dosage of sulfathiazole, the patient was stuporous and confused. Temperature was 98.6° F, pulse 90, respiration 25 and blood pressure 130 mm Hg systolic, 100 mm diastolic. Skin and mucous membranes were dry and icteric. An uremic frost was observed on the skin. There were râles and impaired resonance over the right lower lobe of the lung. Heart appeared normal. Abdomen was distended. There was slight tenderness in the flanks. The right kidney was just palpable. Reflexes were sluggish. Chvostek's sign of tetany was present.

A summary of the blood studies appears in table 1. It will be noted that there was initial hemoconcentration. Polymorphonuclear leukocytosis was present on every examination, rising as high as 37,000 without any evidence of infection. On admission, there was azotemia with acidosis and reduction of serum chloride concentration. Serum phosphorus was 16 mg per cent. Urine was scanty and contained protein (3+), small amounts of bile and urobilin, and a great deal of amorphous debris in which red and white blood cells and large hyaline casts could be seen. No sulfonamide crystals were observed. Roentgenographic examination of the lungs revealed no consolidation.

The patient received 5000 cc of fluids intravenously on the first three days. With a hypotonic glucose-saline mixture and small amounts of sodium lactate, the dehydration and acidosis were relieved. From the fourth day onward the fluid intake was maintained at an average of 3700 cc per day with a total daily sodium chloride

* Received for publication March 13, 1943.

From the Chemical Division, Department of Medicine and the Department of Pathology, Johns Hopkins University and Hospital, Baltimore, Maryland.

TABLE I
Summary of Blood Analyses in Case 1

Days After Sulfonamide	Hematocrit %	W B C thousand	Blood N P N mg %	Serum Cl m eq /l	Serum CO ₂ Comb Power Vols %	Blood Sulfonamide mg %		Serum Protein gm %	Icterus Index
						Free	Total		
7	51	13	320	84	27	4 6	9 2		50
8	41	20	296	86	37				40
9	49		307	84	42			6 5	40
10	43		280	88	49	3 8	8 2		25
11	41	37	304	87	42				25
12	39	31	310		47				20
14	33	30	304	97	43				10
15	25		290					5 8	10
16	25	30	270	116	49	0 8	1 8		
17			256						
18	26	20	192	132	45				
21	22	13	132		44			6 7	
23	20	9	110	146	44	0	0		

intake of 9 grams. The urine output slowly increased from 300 c c on the first day to 1000 c c on the fifth day.

For the first week in the hospital, the patient improved very slightly. Heart rate was very rapid. Digitalis was given, but was discontinued when auriculo-ventricular nodal tachycardia developed. There was bleeding tendency with progressive anemia (hematocrit 33 per cent after one week). The serum chloride was still subnormal.

At the end of one week in the hospital, a large volume of urine was being excreted but accurate measurement was impossible because of incontinence. Blood analyses showed a progressive decrease in the nonprotein nitrogen from this point onward. Serum phosphorus fell to normal, and sulfathiazole disappeared from the blood. The urine remained grossly bloody, and the hematocrit fell steadily despite the appearance of dehydration.

At the same time, the serum chloride concentration began to increase. Salt intake was reduced and then eliminated without any obvious effect on the constantly rising serum chloride. The fluid intake averaged 3800 c c per day. The urine chloride was only 30 m eq /l even when the serum chloride was at its peak.

As the uremia subsided, the patient responded to stimuli and appeared to know what was going on about him. He was unable to speak despite obvious efforts. Movements were purposeful but poorly coordinated. On the last two days of life, when the serum sodium and chloride rose to extreme heights, the patient became stuporous again. He appeared progressively more dehydrated despite the large fluid intake. Breathing was deep and somewhat faster than normal. It became obvious that oral fluids would not suffice to halt the constantly rising salt concentration of the blood. The intravenous administration of 300 c c of salt-free 5 per cent glucose solution was followed by pulmonary edema, which subsided only to return some hours later, terminating in the death of the patient. On the last day of life (sixteenth day in the hospital), serum sodium was 181.5 m eq /l, potassium 5.2 m eq /l, chlorides 146.0 m eq /l, and carbon dioxide combining power 43.8 vols per cent. Blood non-protein nitrogen was 110 mg per cent, urea nitrogen 95 mg per cent and sulfathiazole not present in detectable amounts.

Autopsy. Anatomical Diagnosis: Many focal lesions in renal cortex (obstruction of tubules in cortical rays and of intercalated segments of distal convoluted tubules by hyaline and calcified casts, small foci of interstitial scarring and atrophied

proximal convoluted tubules), changes in widely scattered epithelial cells in glomeruli and tubules of cortex and pyramids (necrosis, calcification and regeneration), scattered thick hyaline foci in arterioles, glomerular capillaries and basement membranes of glomeruli and tubules, organizing thrombi in interlobular renal veins and in a few tiny veins in glomerular layer of adrenal cortex, rupture of tubules into interlobular veins, proliferating epithelium in thrombi, few small hemorrhages, and edema of many cells, fascicular layer of adrenal cortex, history of moderate hypertension, hypoplasia of bone marrow, marked anemia (history), atrophy of central liver cells, jaundice, foci of edema and gliosis in brain, many minute pulmonary hemorrhages, purulent bronchiolitis, lobular pneumonia, and pulmonary edema, slight edema of ankles, atrophy of germinal epithelium, hyperplasia of Sertoli cells and scars in interstitial tissue of testes, metaplasia of epithelium of small pancreatic ducts and dilatation of acini, ulcers over sacrum

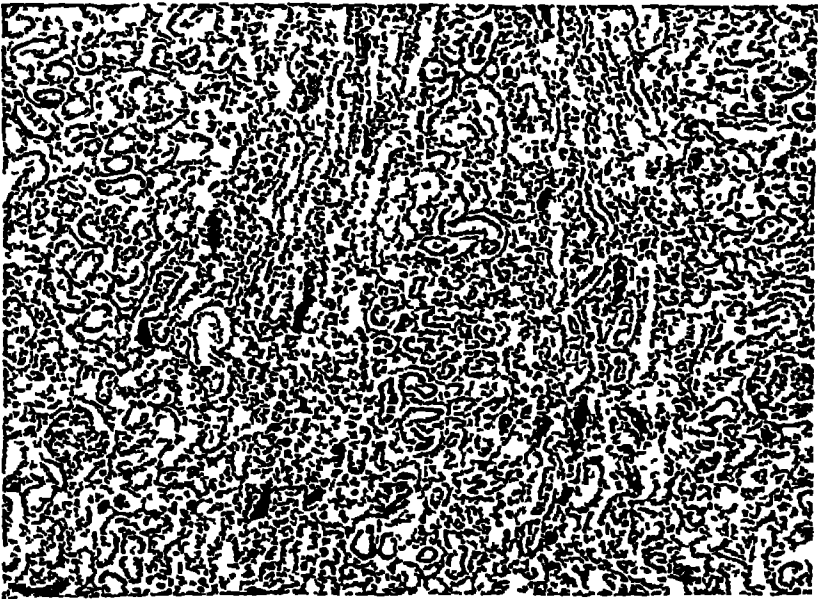


FIG 1 (Case 1) Calcified and hyaline casts within certain tubules of the cortical rays

Kidneys No gross lesions were recognized. Microscopic sections showed long segments of many tubules in each cortical ray to be obstructed and some of them moderately dilated by casts. Some of the casts were hyaline, like coagulated protein. Some casts contained necrotic epithelium and a few leukocytes and many were calcified. A few of the calcified casts lay against the basement membranes of tubules and were covered by a thin layer of regenerated epithelium. A few others appeared to lie partly outside the tubules, in the interstitial tissues. Some of the affected tubules were collecting tubules and more were spiral segments of proximal convoluted tubules.

Besides the obstructed tubules in the cortical rays, there were many other small foci of irregular outline in the renal cortex where tubules were moderately atrophied and separated from each other by loose scar tissue. Still other convoluted tubules contained a few necrotic epithelial cells, and against the basement membranes of some a few cells full of "colloid" drops and a few in mitosis were found. Calcified or hyaline material was present in the intercalated segment of most distal convoluted tubules.

The glomeruli, examined under the oil immersion lens, all showed changes in some of the cells of the visceral and parietal epithelium. There were a few necrotic cells and a few contained "colloid" droplets.

Segments of the basement membranes of many tubules, of Bowman's capsules, and of the glomerular capillaries were irregularly thickened and hyaline, and there were similar small foci in the muscularis of a few arterioles near the glomeruli. In some of Bowman's spaces and between some glomerular capillaries were small collections of hyaline material resembling serum protein. Red blood cells were found in a rare cortical tubule.

In the collecting tubules of the papillae and to a less marked degree in tubules of the boundary zone of the medulla (convoluted and Henle's tubules) there was evidence of damage to the epithelium. A good many scattered cells were necrotic and lay either against the basement membrane or in the tubules. There was considerable new epithelium. Some of the cells were very thin and basophilic and there were numerous mitotic figures.

Deep in the cortex and in the boundary zone, a good many of the interlobular veins were filled with organizing thrombi. Some of these veins communicated with ruptured tubules, and the thrombi contained proliferating tubular epithelium.

Case 2 This 54 year old, colored housewife was brought to the hospital in coma. The patient had been in good general health except for rather frequent attacks of indigestion and abdominal pain. Five days before admission, she complained of generalized aching and fever. On the next day, her physician noted signs of bronchitis and prescribed sulfathiazole in five doses of one-half gram. When the patient failed to improve, sulfapyridine was given for five doses of one-half gram. The temperature fell to normal, but the patient began to vomit and passed little or no urine in the two days before admission.

On admission to the hospital, the patient was described as an obese woman in deep stupor. Temperature was 101.6° F, pulse 140, respirations 28, and blood pressure 62 mm Hg systolic, 40 diastolic. Skin and mucous membranes were deeply icteric and very dry. Breath was uremic. Respirations were deep and labored. The lungs appeared normal. Heart was normal in size and quality of sounds, but there were frequent extrasystoles, sometimes occurring in rapid bursts. There was no tenderness in the flanks, but the patient resisted deep palpation of the right upper quadrant of the abdomen. Tendon reflexes were hyperactive.

There was slight anemia and a leukocytosis of 14,600 with 83 per cent granulocytes. Icteric index was 100. A small amount of murky, brown urine was obtained. This gave strong tests for protein and bile and contained many white and red blood cells with a great variety of casts. No sulfonamide crystals were identified. A summary of the blood analyses is presented in table 2. Serological tests for syphilis were positive.

Although there was much to suggest obstruction of the common bile duct, the surgical consultant felt that because of the patient's precarious condition immediate operation was not justified. On the fourth hospital day, the patient was deeply jaundiced and bleeding from the mucous membranes despite transfusions and vitamin K, but subsequently the jaundice diminished and finally disappeared.

On the first day in the hospital, the patient was given plasma and fluids (hypotonic saline-lactate-glucose mixture) totaling 5 liters. During the subsequent week, the average daily intake was 4.8 liters of fluid with 11 grams of salt. The serum chloride concentration remained subnormal. The urine output on the first three hospital days was 40, 100, and 200 c.c., but during the next week it increased steadily.

At the end of one week in the hospital, the patient began to take some notice of the environment and tried to follow simple commands. Physical status was definitely improved. During the next 11 days, the patient was able to take a liquid diet, and

TABLE II
Summary of Blood Analyses in Case 2

Days After Sulfon- amide	Hemato- crit %	W B C thousand	Blood N P N mg %	Serum Cl m eq /l	Serum CO ₂ Comb Power Vols %	Blood Sulfonamide mg %		Serum Proteins gm %	Serum Bilirubin mg %
						Free	Total		
5	44	15	120	98	28	1 6			
6	32	15	136	95	42	1 4			9 5
7	34	10	132	89	37	1 2	2 1	4 8	10 0
8	34	21	172	92	48				
9	33	27	184	95	41				11 0
12	33	36	208	98	46	1 2	1 9	6 0	5 3
14	31	24	176	105	50	0 8	1 5	6 0	3 1
17	29		124			0 4	1 4		2 7
19	26	12	112						2 1
22			160	160*	43			8 8	1 6
23	33	9	128	139†	44			7 5	
26			88	126	46	0	0		2 2
30			62	116	44				
33			40	110	50			6 4	1 0
40	27		34	105	58				0 9

* Estimated serum sodium 195 m eq /l, total base 210 m eq /l

† Observed serum sodium 174 6 m eq /l, potassium 5 1 m eq /l, calcium 4 8 m eq /l
Observed total base minus magnesium 185 5 m eq /l

parenteral therapy was discontinued. The average daily fluid intake was 2500 cc, with 2 grams of salt, comparable to a "salt-free" regime. Urine output was profuse, but could not be measured because of incontinence. The blood nonprotein nitrogen decreased steadily. The physical condition remained the same save for slight, progressive dehydration until the seventeenth hospital day, when the patient began to have some hyperpnea and lapsed into a deep stupor. On the eighteenth hospital day, the blood chemistry revealed an enormous rise in serum chloride concentration to 160 m eq /l without appreciable reduction of the carbon dioxide combining power, indicating a great increase in serum sodium. Salt-free glucose solution was given intravenously without ill effect. On the next day, serum chloride concentration was 139 m eq /l, serum bicarbonate 187 m eq /l, serum protenate 18 m eq /l (7 5 gm per cent) and serum phosphate 4 5 m eq /l (67 mg per cent), indicating a determined acid concentration of 180 m eq /l, serum sodium was 174 6 m eq /l, potassium 5 1 m eq /l, and calcium 4 8 m eq /l (9 5 mg per cent), indicating a total base minus magnesium of 185 5 m eq /l. It is evident that the primary disturbance was a great increase in the serum sodium and chloride concentration. The urine chloride concentration on this day was only 25 m eq /l, showing a total lack of response to the need for chloride excretion.

During the next two weeks, the patient was given salt-free glucose solution intravenously to make a daily total fluid intake of three liters a day. On this regime the serum chloride concentration slowly fell, reaching normal (105 m eq /l) on the thirty-sixth hospital day. On the same day the blood nonprotein nitrogen was 34 mg per cent. With a liberal fluid intake and a "salt-free" diet, no further chemical disturbances were encountered.

The patient never regained a normal state of consciousness. After the recovery from uremia and hyperchloremia, she was aware of people and appeared to respond suitably to stimuli. She never spoke coherently and movements were jerky and poorly performed.

A constant temperature elevation to 101° F appeared on the fourth week in the hospital. During the fifth week, fever rose to 102° F and remained at this level until death, seldom fluctuating more than a degree in either direction. The patient was intractably distended, but complained of no localized abdominal pain or tenderness. Jaundice did not return. *E. coli*, proteus and an alpha-hemolytic streptococcus were grown from the blood at various times. Administration of a single dose of sulfathiazole was twice followed by a chill and high fever. Sulfadiazine was given without any obvious effect. The patient became gradually weaker and died on the sixty-fourth day in the hospital, 10 weeks after the onset of her illness, seven weeks after the height of the electrolyte changes, and a month after return of the blood sodium, chloride and nonprotein nitrogen to normal.

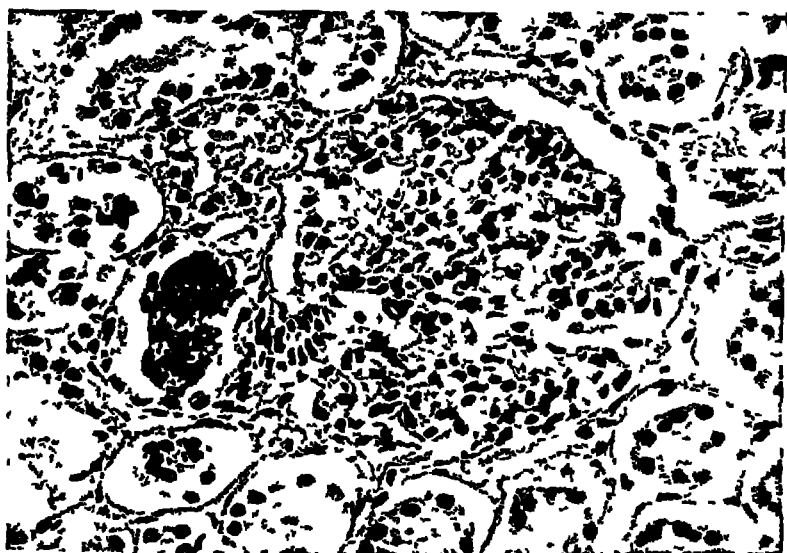


Fig 2 (Case 2) A calcified cast in the intercalated segment of a distal convoluted tubule

Autopsy Anatomical Diagnosis Few small focal lesions in cortex and medulla of kidneys (obstruction and dilatation of tubules, and interstitial scars), foci of edema and gliosis in brain, calcification of small arteries and old infarcts in corpora striata, cholelithiasis and chronic cholecystitis, fractured gall stone in common duct, sinus tract between gall-bladder and abscess in scar tissue about neck of gall-bladder, multilocular abscesses in liver, rupture of abscess, left lobe of liver, serofibrinous peritonitis, partial intestinal obstruction (fibrous adhesions binding loops of ileum), chronic ulcers in ileum proximal to adhesions, otitis media, decubitus ulcers, back, heels, knees, abscesses in muscles of thighs, calcified and caseous tubercles in left bronchial lymph node, extending into left lung, serofibrinous pleurisy, disseminated soft tubercles in spleen, liver, bone marrow, adrenals, and lymph nodes, capillary thrombi and hemorrhages in endometrium, slight hyperplasia of bone marrow, small focus of pulmonary fibrosis, left, fatty liver, slight chronic cystitis, myomata uteri, fibrous pericardial adhesions, moderate arteriosclerosis of aorta.

Kidneys No gross lesions were seen. Sections were made from 16 blocks of tissue. In all of them there were a few tubules in every cortical ray and in the boundary zone of the medulla of every pyramid filled with hyaline material. A rare tubule contained a calcified cast. The obstructed tubules in the boundary zones had the location and size of descending loops of Henle. In the cortical rays some of the affected tubules could be recognized as ascending loops of Henle, and in the cortical labyrinth there were casts in some of the intercalated segments of the distal convoluted tubules. In the cortex of the kidneys there were a few small scattered foci

composed of several moderately atrophied tubules separated by fairly cellular new-looking scar tissue

Case 3 This 19 year old white housewife was admitted because of high fever, stupor and anuria. She had been in good health with no evidence of preëxisting nephritis. Two weeks before admission, when the patient had passed uneventfully through her first pregnancy, labor was induced. Labor was prolonged and several vaginal examinations were said to have been made without adequate sterile technic. Because of some fever the patient was given sulfathiazole 6 grams per day for four days post-partum. The patient improved slowly after a difficult delivery, and the temperature returned to normal. Because of nausea and occasional vomiting, sulfathiazole administration was stopped on the fourth day post-partum. On the seventh and eighth days, there was intermittent fever of 101° F with very questionable evidence of pelvic infection and no other obvious source of fever. Sulfathiazole was again given in doses of 7 grams on the ninth day and 3 grams on the next day. Temperature promptly rose to 105.4° F, pulse rose steadily to over 170 per minute and the blood pressure fell to 80 mm Hg systolic, 40 mm diastolic. The patient became deeply stuporous and unresponsive. Very little urine was passed for four days. Sulfathiazole was discontinued when no adequate evidence of infection was found. Fluids and blood were given by vein.

On the twelfth day post-partum, the patient was admitted to the medical ward. She was deeply stuporous. There were fever, tachycardia and dehydration. Muscles showed a coarse, jerky tremor. Chvostek's and Trousseau's signs of tetany were absent. Reflexes were hyperactive, Babinski's sign not present. The usual post-partum changes in breasts and uterus were noted.

The red blood cell count was 3.85 million and a white blood cell count was 14,000 with polymorphonuclear cell increase. Urine was dilute and contained protein (3+), many white blood cells and a few red blood cells. No crystals were seen. The blood nonprotein nitrogen was 100 mg per cent, free sulfathiazole concentration was 88 mg per cent, with a very high total drug level of 188 mg per cent. Serum chloride was reduced to 89 m eq/l and the carbon dioxide combining power to 23 vols per cent. Serological tests for syphilis were negative.

Because of dehydration and acidosis, the patient was given by vein 5000 c c of fluids containing 10 grams of salt as well as glucose, on the first day on the medical ward. The acidosis was improved following the administration of sodium lactate. Because of the development of hyperchloremia in the previous patients, this patient was then given only 4 grams of salt per day for the two subsequent days. Liberal amounts of fluid were given by vein, and the urine output increased to over 1000 c c per day. On this régime, the serum chloride remained below 90 m eq/l. The salt intake was increased to 12 grams and 8 grams on the next two days, raising the serum chloride concentration to 106.4 m eq/l. Blood nonprotein nitrogen fell rapidly to 44 mg per cent.

The patient was then placed on a salt-poor régime (4 grams of salt with 4000 c c. of fluid). In three days, the serum chloride concentration rose to 117.5 m eq/l. The salt intake was reduced to approximately 2.5 grams per day (a "salt-free" régime). On the next day, the serum chloride rose to 124 m eq/l with the spinal fluid chloride concentration 161.2 m eq/l. The blood nonprotein nitrogen was 56 mg per cent. The slowly rising temperature reached 105° F.

The fluid intake was raised to 5000 c c per day, approximately half of this amount being given intravenously as 5 per cent glucose solution. The temperature fell and the serum chloride concentration gradually decreased to normal (105 m eq) during the next week. At this time, the serum carbon dioxide combining power was 53 volumes per cent and the blood nonprotein nitrogen was 26 mg per cent.

During the development of hyperchloremia when the serum chlorides were 117.5 m eq /l, the urine chloride concentration was 44 m eq /l and the total urine chloride output was 2.18 grams in 24 hours. Three days later, when the serum chloride concentration was 122.5 m eq /l, the urine chloride concentration was 44.4 m eq /l, and the total urine chloride output was 2.17 grams in 24 hours. During the fall in serum chloride concentration, there was only a slight increase in urine chloride concentration and scarcely any change in the daily output of chloride. Apparently, the large water intake first produced a dilution of the extracellular electrolytes rather than an increased chloride output. After several days, the patient reached a nice balance of intake and output.

When the serum chloride fell to 110 m eq /l and the fever disappeared, a mannitol clearance was performed*. At this time, the urine volume and chloride concentration were the same as during the height of the hyperchloremia. This test showed an average reduction of glomerular filtration to 30 per cent of the expected normal value. Parallel studies of serum and urine chlorides showed that 97 per cent of the chloride in this glomerular filtrate was reabsorbed while only 90 per cent of the water was reabsorbed. Phenolsulfonphthalein excretion was 45 per cent in two hours. On the next day, urea clearance was 29 cc per min. The nonprotein nitrogen was 34 mg per cent.

As the uremia and hyperchloremia disappeared, the patient's responsiveness to the environment returned, but gross neurological defects became more obvious. It was noted that the patient failed to move the left arm and the right hand. The tongue and jaw also could not be moved normally. All of these parts showed a coarse, jerky tremor. In the legs, the tremor had diminished and voluntary movement was improving. The tremor was aggravated by attempts at movement. Swallowing of food was difficult. The patient smiled and wept on appropriate occasions.

During the next month, atrophy of the right thenar eminence and of muscles of the right leg became obvious. The electrical reaction of degeneration was demonstrated in the right opponens pollicis. The left fifth finger was held in full extension, whereas the other fingers were flexed. The left wrist was held in extension. Elsewhere, a steady return of function was evident. Muscles were atonic, movements were jerky, and reflexes were hypoactive, but gross movement of all four extremities was possible. Babinski's sign was absent.

Three months after the sulfathiazole administration, the patient had regained fair strength and control of most of her muscles, although tremor and poor coordination prevented any fine movements. For several weeks, she had made halting efforts to speak, and words were becoming clearer. With the return of speech, the patient confirmed the impression that no sensory loss had occurred. She remained very euphoric.

Case 4 This 63 year old white paper-hanger was admitted to the hospital because of epigastric pain and anemia. His health had been good until two months before admission, when he noted the gradual onset of deep, gnawing epigastric pain, unrelated to meals, but relieved by soda. One month later, the pain was worse and the stools became dark in color. The patient complained of spells of weakness and faintness.

The only abnormalities on examination were pallor and tachycardia. Blood pressure was 118 mm Hg systolic, 68 diastolic. The red blood cell count was 1,800,000 without change in cell size or color. Stools were tarry and gave strongly positive chemical tests for blood. Urine had a specific gravity of 1.020 and contained no sugar or protein, occasional white blood cells, but no red blood cells or casts. Roentgenograms demonstrated a deep ulcer on the lesser curvature of the stomach.

* With the kind assistance of Dr. L. V. Newman.

The blood nonprotein nitrogen was 49 mg per cent* Serum chloride was 106.6 m eq / l , carbon dioxide combining power 56 volumes per cent and protein 4.6 grams per cent

The patient improved briefly and then suffered an exsanguinating hemorrhage, during which six liters of blood were necessary to keep the systolic blood pressure above 90 mm of mercury After two days without any cessation of bleeding, a subtotal gastrectomy and anterior Polya anastomosis were performed Sulfathiazole powder was applied locally, and sodium sulfathiazole was given intravenously in four doses of 4 grams over a period of 48 hours During these two days, the patient received 5500 c c of fluid by vein, of which approximately one-third was physiological sodium chloride solution One hour after the last sulfathiazole injection, the blood sulfathiazole concentration was high (14.9 mg per cent) At this time, the blood nonprotein nitrogen was 80 mg per cent, serum chloride was 95.6 m eq / l , carbon dioxide combining power was 74.8 volumes per cent, and plasma protein was 6.3 gm per cent Only 175 c c of urine were passed on the next day, but the blood nonprotein nitrogen did not rise and the free sulfathiazole level fell to 6.3 mg per cent Following this the urine volume gradually increased The urine contained protein, a few red and white blood cells, many casts and numerous sulfathiazole crystals The free sulfathiazole level fell to 1.8 mg per cent on the next day but serum chloride concentration rose to 120 m eq / l The patient had been receiving 4 liters of parenteral fluid each day, containing 9 grams of sodium chloride (38 m eq / l) When the high serum chloride concentration was noted, salt intake was eliminated save for that contained in transfusions of blood Despite the low sodium chloride intake and the liberal fluid intake, the serum chloride concentration on the next day was 142 m eq / l The carbon dioxide combining power was never below the normal level of 55 volumes per cent (bicarbonate 23.5 m eq / l) Blood nonprotein nitrogen remained between 80 and 90 mg per cent The urine output was profuse but could not be measured because of incontinence

The patient's condition was most precarious during the hemorrhage, and he failed to rally after operation With the hyperchloremia, he became irrational and stuporous, and his breathing was more labored At the same time, evidence of localized peritonitis was noted and it appeared that a leak had developed about the gastroenterostomy This was repaired, but the patient died on the next day (the eighth day in the hospital) Blood drawn 12 hours before death had a nonprotein nitrogen of 82 mg per cent and serum chlorides 142 m eq / l

Autopsy Anatomical Diagnosis Chronic gastric ulcer (removed at operation) serofibrinopurulent peritonitis, marked anemia (history of massive hemorrhages), atrophy of central liver cells, minute hemorrhages in adrenals and islands of Langerhans, purulent bronchitis and slight lobular pneumonia, apical pleural scars, emphysema, moderate arteriosclerosis, history of sulfathiazole therapy, blood transfusions and renal insufficiency, marked dilatation of terminal collecting ducts in some renal papillae, obstruction and dilatation of few tubules in renal papillae, pyramids and cortex by casts (granular, hyaline and calcified material, red blood cells and hemoglobin)

Kidneys No gross lesions were seen Sections from 23 blocks were examined microscopically There were a few minute areas of atrophied tubules and hyaline glomeruli, old lesions probably caused by intrarenal arteriosclerosis There was no evidence of wide-spread damage to the renal epithelium

In several papillae the large collecting tubules were greatly dilated although no crystals or other obstructions remained in the stained preparations, and no casts

* The influence of gastrointestinal bleeding in raising the blood nonprotein nitrogen concentration makes the interpretation of this determination difficult throughout this particular course

were seen in the gross specimen. Some of the terminal ducts, however, were dilated and filled with red blood cells and granules of hemoglobin.

In addition there were a few obstructed and slightly to moderately dilated tubules scattered higher in the papillae and medulla, and in the renal cortex. Some of these contained hyaline and granular material and a few contained calcified casts.

The brain was not examined.

Case 5 This 17 year old white girl was brought to the hospital in coma. She had been in good health save for one episode of dysphagia and regurgitation three years before. Three weeks before admission, she developed a sore throat which persisted for several days. One week later, because of persistent sore throat and fever, her physician prescribed a sulfa-drug which was taken for three days. The family did not recall the specific name of the drug and no information could be obtained from the physician. The patient began to vomit and finally could not retain even fluids. Her mental state was one of confusion progressing to delirium and then coma. Parenteral fluids in undetermined amounts were given without any benefit. No data on the urine output are available. Parotitis developed on the left side. At this time, she was brought from Tennessee to this hospital.

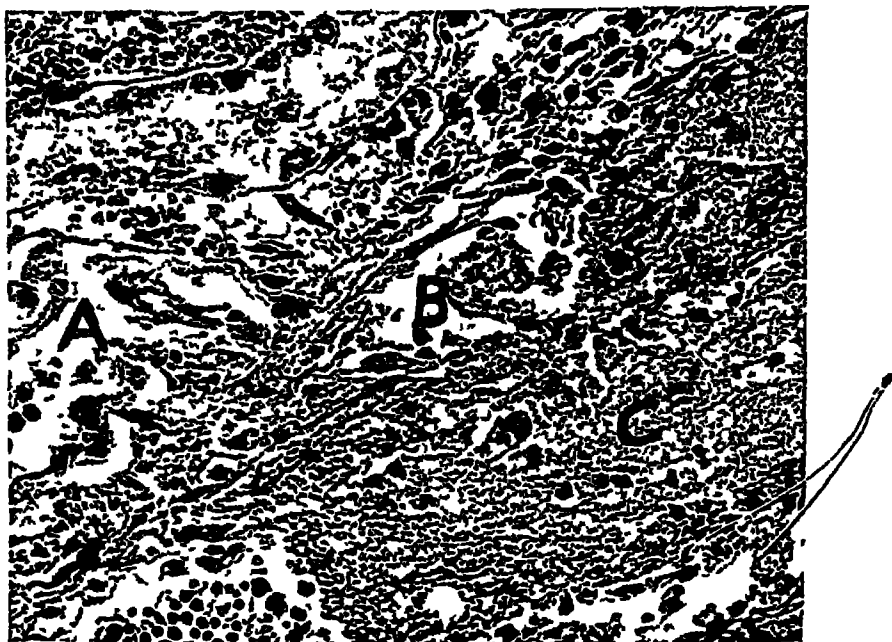


FIG 3 (Case 5) A indicates a tubule lined by regenerated epithelium. B shows the lumen of another tubule. C is a thrombus in an interlobular vein. The tubule and vein communicate and epithelial cells are growing in thrombus.

On admission three weeks after alleged sulfonamide medication, the patient was a seriously ill young girl, stuporous and unresponsive. Temperature was 101.8° F, respiration 40, pulse 100, and blood pressure 132 mm Hg systolic, 90 diastolic. Skin and mucous membranes were dry. The left parotid gland was tensely swollen and pus could be expressed from the parotid duct. Ocular fundi, heart, and lungs appeared normal. Minimal pitting edema was observed over the tibiae. No abnormalities were made out on neurological examination.

Blood examination revealed 4,070,000 red blood cells per cu mm, with 13,000 white blood cells, of which 93 per cent were granulocytes. Icteric index was normal. Serological tests for syphilis were negative. Urine had a specific gravity of 1.010, was neutral to litmus and contained a trace of protein, a few white blood cells, rare

red blood cells, and rare granular and hyaline casts. No crystals or large casts were seen. Urine volume could not be measured because of incontinence, but was not obviously reduced. Lumbar puncture revealed clear fluid, with no increase in cells or protein. A chloride determination on the spinal fluid could not be titrated, indicating a chloride concentration in excess of 150 m eq/l.

The patient grew rapidly worse and died 24 hours after admission. She received 5 grams of sodium sulfadiazine intravenously without any obvious effect. Six hours before death, the blood chemistry reports revealed blood nonprotein nitrogen 112 mg per cent, serum chloride above 150 m eq/l, carbon dioxide combining power 27 volumes per cent. The patient was given glucose solution intravenously, but the appearance of pulmonary edema prevented the administration of large amounts. At death, blood chemistry revealed nonprotein nitrogen 120 mg per cent, serum chloride 141.2 m eq/l, carbon dioxide combining power 26.8 volumes per cent and serum sodium 173.8 m eq/l. Urine contained 27 m eq chloride per liter.

Autopsy Anatomical Diagnosis Dilatation and hypertrophy of esophagus, chronic inflammation, edema and small venous thrombi in submucosa of larynx and esophagus, purulent cellulitis, subcutaneous tissues about left parotid gland, ulcerative fibrinopurulent colitis, and edema of stomach submucosa, areas of necrosis of mucosa and submucosa of vagina and cervix uteri, thrombi in intra and extra vaginal and uterine veins, interlobular renal arteries and veins, and adrenal capillaries, emboli in small pulmonary arteries, small infarcts in adrenals (few), and kidneys (many), marked cloudy swelling of renal epithelium and edema of interstitial tissue, necrosis and regeneration of scattered epithelial cells in glomeruli and tubules of kidneys, ascites, hydrothorax, hydropericardium (slight) and pulmonary edema, small area of fibrinous pleurisy, left, edema, gliosis and minute hemorrhages in medulla of cerebellum, fat in liver cells, hemorrhages and marked hyalinization of arterioles in spleen.

Kidneys Grossly the kidneys were swollen, soft and pale. On the external and cut surfaces there were a good many scattered areas a few millimeters in diameter which were indistinctly outlined, opaque, and partly outlined by reddish borders.

Sections were cut from 20 different blocks of tissue. In 11 sections organizing thrombi were found in interlobular veins or arteries or both. More veins than arteries were occluded. Most of the thrombosed vessels were deep in the cortex and in the boundary zone. Small infarcts, a few millimeters wide, were present in six of the sections. The interstitial tissues of cortex and medulla were coarse meshed and spread apart, due evidently to edema which escaped into the fixing fluids. Damaged tubules, some containing casts and lined by regenerating epithelium, were found to have ruptured into some of the veins which contained thrombi, and the latter showed strands and small masses of proliferating tubular epithelium.

The epithelial cells especially of the glomeruli and of the proximal convoluted tubules showed marked cloudy swelling. Hyaline casts were present in relatively few tubules, most of which were ascending loops of Henle in the cortical rays, but some of the tubules in the pyramids and a few convoluted tubules also contained casts.

Necrotic and regenerating epithelial cells in small numbers were found in glomeruli and in various tubules of cortex and medulla.

ETIOLOGY

In the first three cases, sulfathiazole probably precipitated the renal changes which led to the hyperchloremia. These patients were previously active and apparently in good health. Anuria and uremia followed several days of sulfathiazole administration. Hyperchloremia followed as a larger

volume of urine was excreted and as the blood nonprotein nitrogen was decreasing

In Case 4, there are several possible factors. The patient received many transfusions of stored, citrated blood within a few days. There was transient shock during the hemorrhage. The loss of gastric secretion produced hypochloremia and alkalosis at one time. Finally, the patient received a large dose of sulfathiazole, with high blood levels, crystalluria, and subsequent anuria. As the urine volume increased, the patient developed hyperchloremia. Apparently sulfathiazole precipitated the anuria and subsequent hyperchloremia, but there were other possible factors.

In Case 5, the history was very similar to the other patients', with a rather mild infection said to have been treated with a sulfa-drug, followed by vomiting, stupor, uremia, and terminal hyperchloremia. In view of the ulcerative vaginal lesions and the presence of gross thrombi in pelvic veins, the possibility must be considered that the intrarenal thrombi may have extended up from the pelvic vessels.

CLINICAL OBSERVATIONS

The first three patients were critically ill during the initial period of anuria and uremia. This was followed by a period of slow improvement, as the uremia subsided. When the serum sodium and chloride concentration rose to excessively high levels, the patients appeared dehydrated, and hyperpnea was noted without a significant decrease in the carbon dioxide combining power of the serum. The mental condition of the patients deteriorated at high serum electrolyte levels. Two patients died with acute pulmonary edema after cautious administration of salt-free fluids at the height of the electrolyte concentration. Two others tolerated a large amount of intravenous fluid and survived.

Three of the patients died before the blood chemistry returned to normal. None of these three patients regained a normal state of consciousness, nor could they speak or make coordinated movements. Because of the chemical disturbances, however, it was difficult to evaluate the mental and neurological changes. Two patients were observed for many weeks after the blood chemistry became normal. They both had persistent difficulty with speech and coordination. Since the neurological changes were most pronounced in a patient who never had a very marked elevation of serum sodium and chloride, the sulfonamide drug may initiate the injury to the central nervous system.

It is worthy of note that the first three patients had a high polymorphonuclear leukocytosis which appeared to be related in time to the sulfathiazole intoxication and not to any obvious infection.

CHEMICAL CHANGES

The distinctive chemical change was the rapid and unusual increase in serum sodium and chloride concentration. This hyperchloremia was as-

sociated with only a relatively insignificant reduction of serum bicarbonate as measured by the carbon dioxide combining power. There was a gross increase of the total serum electrolyte concentration, normally "one of the most jealously guarded constants of the organism"¹. The high spinal fluid chloride in Cases 3 and 5 indicates that the increased electrolyte concentration was shared by the body fluids other than serum, as might be expected on theoretical grounds.

It may not be assumed that there was a similar increase in the total mass of electrolyte in the body. Indeed, the patients appeared dehydrated at the peak of electrolyte concentration, suggesting a decreased volume of extracellular fluid, which would more or less balance the increased electrolyte concentration. These circumstances suggest that the primary disturbance was a loss of water without a corresponding amount of electrolyte.

The large urine volume of very low, fixed chloride concentration supports the idea that water was being lost in excess of sodium chloride and points to the kidney as the origin of the disturbance. In one patient a mannitol clearance test, performed while the electrolyte disturbance was subsiding, showed a reduction of glomerular filtration to 30 per cent of normal. Simultaneous determination of serum and urine chlorides indicated that 97 per cent of the chloride in this glomerular filtrate was reabsorbed, whereas only 90 per cent of the water was reabsorbed. These data, suggesting a greatly reduced volume of glomerular filtrate and a failure of the tubules to reabsorb the normal proportion of water, afford a plausible explanation for the large volume of urine of very low salt content.

The rise of serum chloride concentration above normal was observed only after the daily urine output became large. For the first week in the hospital, Cases 1 and 2 received considerable amounts of salt and water to overcome the initial dehydration and oliguria. The serum chloride remained low, since the fluids given were hypotonic and the oliguric kidney could exert little influence on the composition of the body fluids. When the urine volume increased, the blood nonprotein nitrogen began to fall, and simultaneously the serum chloride rose*. There was no superficial change in the character of the urine which remained dilute and neutral in reaction.

It would therefore seem that the large amounts of salt and water given to several anuric patients had little effect on the subsequent rise of serum sodium and chloride concentration. The rise was dependent on the secretion of a large volume of urine, with excessive loss of water without salt in the urine and the failure to replace this water without salt. Under these conditions, the serum electrolyte concentration must increase regardless of the previous state of hydration. Any salt given after the urine volume becomes large, however, definitely aggravates the electrolyte disturbance.

Serum electrolyte changes of the type and degree seen in these patients are not ordinarily observed in chronic nephritis. Hyperchloremia is un-

* In Cases 1, 2, and 3. In Case 4 the blood nonprotein nitrogen was difficult to interpret because of gastrointestinal hemorrhage. In Case 5, data are not available.

common in chronic retentive nephritis, and serum base concentration is almost without exception normal or low² Slight elevation of the serum chloride concentration is the rule in the nephrotic syndrome but is not accompanied by any appreciable increase in serum base concentration³ If an adequate fluid intake is maintained, excessive salt intake does not ordinarily raise the serum chloride concentration except as it displaces bicarbonate, with the serum sodium concentration approximately normal In other words, even in severe chronic nephritis, when sodium chloride is retained in the body a proportional amount of water is retained with it so as to keep the concentration of sodium near normal Retention of salt thus results in edema rather than hyperchloremia This relationship was lost in the patients here reported in whom water was lost so much in excess of salt To be sure, in severe chronic nephritis with a normal serum concentration, the maximum urinary chloride concentration is usually considerably higher than in the cases here reported, though rarely approaching the serum concentration⁴

Although the rapid onset, the extreme degree of hyperchloremia and the very high serum sodium levels in these patients are unique, other cases with some points of similarity have been described Butler, Wilson and Farber⁵ described persistent dehydration with hyperchloremia in infants These changes were chronic and were associated with acidosis and no elevation of serum sodium Calcification was found about the kidney tubules Butler, Wilson and Farber⁵ and Albright, Consolazio, Coombs, Sulkowitch and Talbot⁶ have reported similar changes in older children, associated with rickets and dwarfism In most of these patients, the cause of the calcification about the kidney tubules was not known In one case, hyperparathyroidism was apparently the initiating factor The most extensive calcification in all of these patients was about and within the collecting tubules, although some changes were evident in other portions of the tubules

DISCUSSION OF RENAL LESIONS

Hematuria, oliguria and azotemia have frequently been observed in man and in experimental animals following the administration of sulfonamides, and these signs and symptoms, when investigated, have usually been found to be associated with obstruction due to precipitation of crystals in renal tubules or ureters, or in both.

The occurrence of high serum sodium and chloride concentrations after sulfonamide medication, developing and progressing while azotemia and oliguria decreased, has not been described before Such a specific functional disturbance suggests a corresponding specific renal lesion, and the changes found in the kidneys of Cases 1 and 2 point to the intercalated segments of the distal convoluted tubules, the spiral portions of the proximal convoluted tubule, the collecting cortical tubules, or the ascending limb of Henle's loop as possible sites of the specific disturbance In the other two cases which

were examined microscopically it was impossible to correlate the salt retention with specific localized lesions

The occurrence of thrombi in intrarenal veins (Cases 1 and 5) due to sulfonamide administration has not been described before in man. It has been seen in the monkey following sulfapyridine medication⁷ and in dogs which were given sulfadiazine.⁸

In one of our cases (Case 1) in which thrombi formed in the intrarenal veins, the only sulfonamide given to the patient was sulfathiazole. This is of some interest because Climenko and Wright⁷ found renal thrombi in their monkeys after sulfapyridine, but never in the sulfathiazole animals. In our other case (Case 5) which showed thrombi in renal vessels, the exact nature of the sulfonamide which the patient took, and the dose could not be determined, and thus it is possible that the lesions found were due to some other drug. Moreover, there were thrombi in many small renal veins and arteries, and there were thrombi in vessels other than those in the kidneys. Most of the changes in the kidneys themselves were probably caused solely by the vascular occlusions.

The damaged and ruptured tubules in the boundary zone, associated with thrombosed interlobular veins and with proliferating tubular epithelium in the thrombi (Cases 1 and 5), are apparently identical with similar lesions described by Dunn, Gillespie, and Niven⁹ as occurring in two cases of crush syndrome. One of these patients lived for nine days and was treated with sulfapyridine. This report does not state whether the second patient received sulfonamide medication, but it would seem possible that these tubulovenous lesions may have been related to the therapy rather than to the crushing injuries.

The pathogenesis of intrarenal thrombus formation following sulfonamide therapy is not clear, but it may be suggested that precipitated crystals could easily project through the tubular epithelium and into the very thin walled interlobular veins, and in this way might cause thrombi to develop.

TREATMENT OF ELECTROLYTE DISTURBANCE

During the stage of anuria, there is little danger of hyperchloremia. The use of very hypotonic fluids at this time serves only to depress the already low electrolyte concentration. A slightly hypotonic mixture of sodium chloride and lactate, with glucose as needed, seems to be effective.

As the urine volume increases, the fluid intake should be maintained at a level of at least 3000 cc a day. Salt intake should be eliminated. In some cases a large volume of intravenous salt-free fluid may be needed daily to avoid hyperchloremia.

Not every patient with sulfathiazole-induced oliguria develops hyperchloremia. On the other hand, when symptoms become prominent, the hyperchloremia is already far advanced and treatment may be ineffectual. The ideal method is to follow the serum chloride concentration.

SUMMARY

1 Three patients with severe sulfathiazole intoxication and two patients with probable sulfonamide poisoning are described

2 All of the patients developed an unusual increase in serum sodium and chloride concentration. When continuous observations were made, the electrolyte disturbance appeared while oliguria and nitrogen retention diminished. The excessive height of the serum electrolyte concentration probably contributed to the death of two patients.

3 The renal lesions found in two cases suggest that the dissociation of salt and water excretion may be related to changes in certain specific portions of the tubule.

4 There were thrombi in interlobular veins in two cases. In one of these, thrombi in both interlobular arteries and veins were numerous and probably produced the renal lesions recognized in this case. In both cases, the thrombosed veins were associated with ruptured tubules and the proliferation of tubular epithelium in the thrombi. Both patients developed moderate hypertension.

5 Clinically, there was evidence of cerebral damage. In the two patients who survived the uremia and hyperchloremia, the signs of injury to the central nervous system persisted, with slow and incomplete recovery. In the brains which were examined, areas of edema and gliosis were found, together with small hemorrhages in one case.

BIBLIOGRAPHY

- 1 PETERS, J P, and VAN SLYKE, D D. Quantitative clinical chemistry, 1931, The Williams and Wilkins Company, Baltimore, 1, 761.
- 2 PETERS, J P, WAKEMAN, A M, EISENMAN, A J, and LEE, C. Total acid-base equilibrium of plasma in health and disease. X The acidosis of nephritis, *Jr Clin Invest*, 1929, vi, 517.
- 3 PETERS, J P, WAKEMAN, A M, EISENMAN, A J, and LEE, C. Total acid-base equilibrium of plasma in health and disease. XII A study of renal edema, *Jr Clin Invest*, 1929, vi, 577.
- 4 PETERS, J P, WAKEMAN, A M, and LEE, C. Total acid-base equilibrium of plasma in health and disease. XI Hypochloremia and total salt deficiency in nephritis, *Jr Clin Invest*, 1929, vi, 551.
- 5 BUTLER, A M, WILSON, J L, and FARBER, S. Dehydration and acidosis with calcification at the renal tubules, *Jr Pediat*, 1936, viii, 489.
- 6 ALBRIGHT, F, CONSOLAZIO, W V, COOMBS, F S, SULKOWITCH, H W, and TALBOT, J H. Metabolic studies and therapy in a case of nephrocalcinosis with rickets and dwarfism, *Bull Johns Hopkins Hosp*, 1940, lxxvi, 7.
- 7 CLIMENKO, D R, and WRIGHT, A W. Effects of continued administration of sulfathiazole and sulfapyridine in monkeys, *Arch Path*, 1941, xxxii, 794.
- 8 MAISEL, B, McSWAIN, B, and GLENN, F. Lesions produced with sulfadiazine, *Proc. Soc. Exper Biol and Med*, 1942, xlix, 715.
- 9 DUNN, J, GILLESPIE, M, and NIVEN, J S F. Renal lesions in two cases of crush syndrome, *Lancet*, 1941, ii, 549.

LEUKEMIA: THE RELATIVE INCIDENCE OF ITS VARIOUS FORMS, AND THEIR RESPONSE TO RADIATION THERAPY *

By FRANK H BETHELL, M D , F A C P , *Ann Arbor, Michigan*

WERE one resigned to the acceptance of the cause and cure of leukemia as a problem of the inscrutable future, requiring for its solution weapons not yet conceived in imagination, then the study of the cytologic features underlying its varied clinical manifestations would constitute little more than an exercise in morbid histology. If, on the other hand, one believes that an understanding of the cell types involved in leukemic change is a prerequisite to the progressive clarification of the problem in its entirety, then detailed cytologic analysis becomes a potentially profitable undertaking.

The purpose of this communication is to present a series of cases of leukemia, all of which have been subjected to the same criteria of differentiation, and to indicate the relative frequency of the several types of cellular involvement which have been observed. Consideration is also given to the sex and age incidence and to the degree of response of the patients' disease to radiation therapy, but detailed presentation of clinical information and quantitative blood changes is deferred for later publication.

The series to be reported is composed of 495 cases examined at the Simpson Memorial Institute between July 1, 1927 and December 31, 1941, a period of 14½ years. For the purposes of this and subsequent studies the records of all the patients were analyzed and data supplied by the history, physical examination and laboratory procedures, including biopsy and necropsy, were tabulated. In 262 cases, including those in which the original diagnosis appeared to be in reasonable doubt, the blood and, when available, the marrow films were reexamined. In 19 per cent of the cases necropsy was performed and the presence of leukemia was confirmed, although designation of specific type, as here reported, was not usually made. Lymph node biopsy was performed in only a negligible number of instances, except in cases of lymphosarcoma cell leukemia. Marrow was examined during life in but a few instances prior to 1936. After this date such study was carried out in practically every case, except in young children with leukemic lymphoblastic leukemia and in patients with lymphocytic and myelocytic leukemia in leukemic phase. Of these groups marrow examinations were made in about half the cases.

It has seemed possible to classify the great majority and perhaps all of the cases observed according to three parent cell types: the lymphoblast, the myeloblast, and the undifferentiated or but slightly differentiated reticulum

* Read at the St. Paul meeting of the American College of Physicians April 21 1942.
From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan

cell (histioblast or histiocyte). These main divisions of leukemia are designated, respectively, as lymphogenous, myelogenous and histogenous (chart 1). The subdivision of lymphogenous leukemia into lymphoblastic, lymphocytic, and lymphosarcoma cell types, has been discussed in an earlier communication, and these forms of the disease will not be considered here, except for purposes of comparison.¹

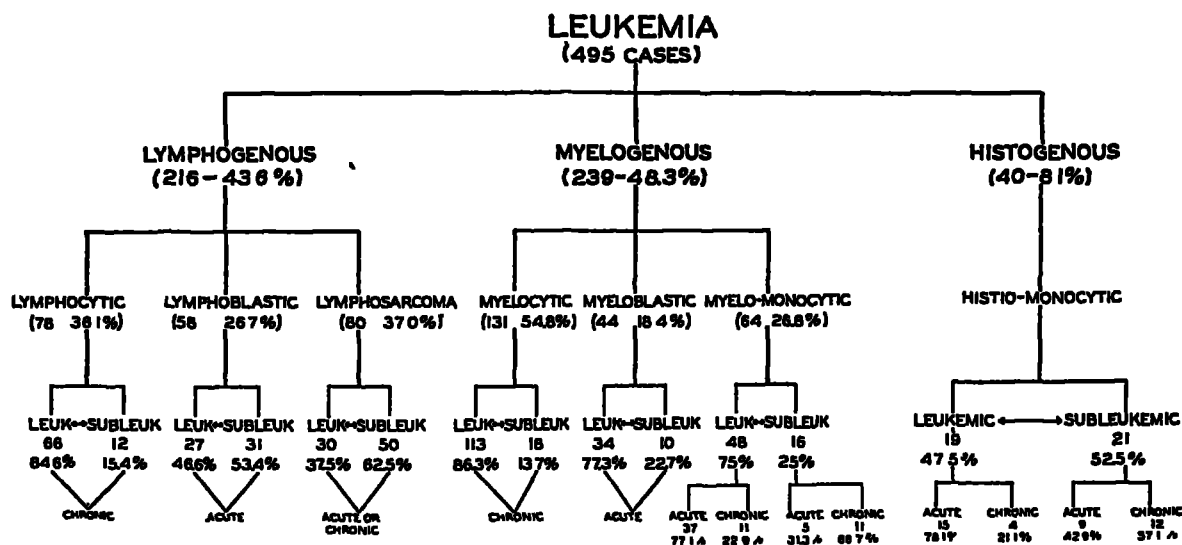


CHART 1

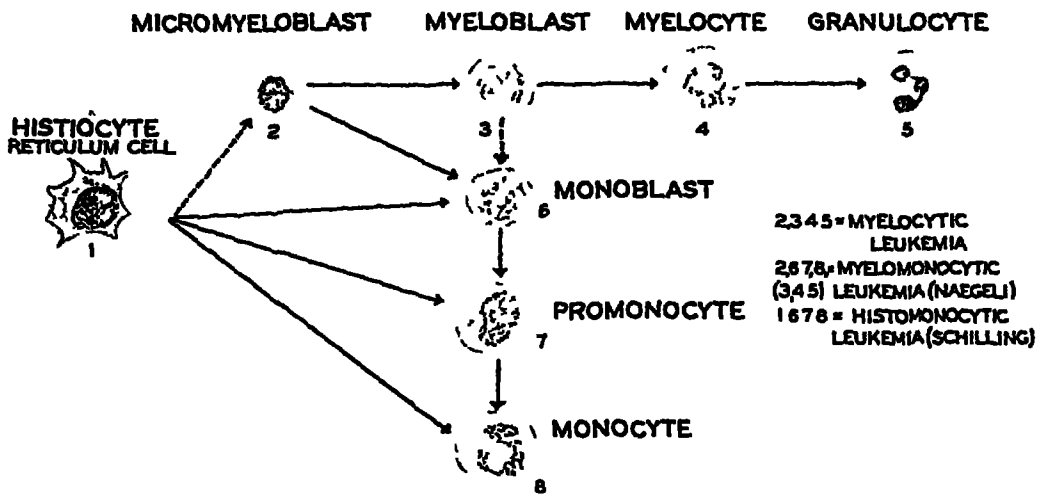
The consideration of varieties of myelogenous leukemia is based on the view expounded by Naegeli,² and supported by observations made on the patients of this series, that the myeloblast, or its immediate precursor, the micromyeloblast, may undergo leukemic proliferation with little or no evidence of maturation, or there may be development into the myelocyte and later stages, or there may be transition to the monoblast with subsequent formation of older forms of the monocyte series. These three forms of myelogenous leukemia are termed, respectively, myeloblastic, myelocytic and myelomonocytic. Most of the rarer forms of leukemia, such as erythroleukemia, and eosinophilic, basophilic, and probably megakaryocytic leukemia are members of the myelogenous group. Plasma cell leukemia, on the other hand, as suggested by Richter³ may be related to the lymphogenous types.

There remains a group of cases of leukemia which exhibit no evidence of lymphoblastic or myeloblastic involvement, but are characterized by generalized proliferation of cells of reticuloendothelial origin. Monocytes in their several stages of development are commonly found in the circulating blood of such patients, and frequently there also occurs larger "histiocytic" forms. This type of leukemia is here called histiomonocytic (figure 1).

A critical discussion of monocytic leukemia with a review of the very extensive literature on the subject is given by Downey.⁴ That form which is believed to arise from the myeloblast he designates as the Naegeli type,

whereas leukemia of reticuloendothelial origin is termed the Schilling type of monocytic leukemia. According to Downey, "The end products (ripe monocytes) might have identical morphology but the intermediate and younger forms would be different." However, accurate diagnosis often requires marrow examination and one hesitates to identify a case of leukemia as of histiomonocytic type without pathologic evidence of uncontrolled reticulum cell hyperplasia.

Watkins and Hall⁵ have adopted Downey's differentiation of monocytic leukemia and in accordance with it have classified the cases seen at the Mayo Clinic during a 10 year period. These authors describe in detail the



THE RELATIONSHIPS OF MYELOCYTIC, MYELOMONOCYTIC (NAEGELI)
AND HISTOMONOCYTIC (SCHILLING) LEUKEMIA

FIG 1

morphology of the cells seen in both types of monocytic leukemia, as well as marrow changes characteristic of the two diseases. In general, the peripheral blood in cases of myelomonocytic leukemia (Naegeli) contains a predominance of monocytes in various stages of maturity together with a small (sometimes large) number of myeloblasts and young myelocytes. Monoblasts differ from myeloblasts, in Wright stained films, in that the nuclear chromatin of the former is arranged in a fine transparent network, the nucleoli are quite inconspicuous and the cytoplasm is more plentiful and often contains fine red granules at a stage of nuclear development when granulation is not found in the myeloblast. In histiomonocytic leukemia (Schilling) myeloblasts are absent from the peripheral blood, although an

occasional myelocyte may be found. Monocytes, often quite mature in appearance, predominate, and larger histiocytes may be present. In the latter, the chromatin of the nucleus is arranged in a relatively coarse network, the nucleoli are indistinct in the earlier forms but small and clearly outlined in the later stages. The cytoplasm is blue-gray and often contains

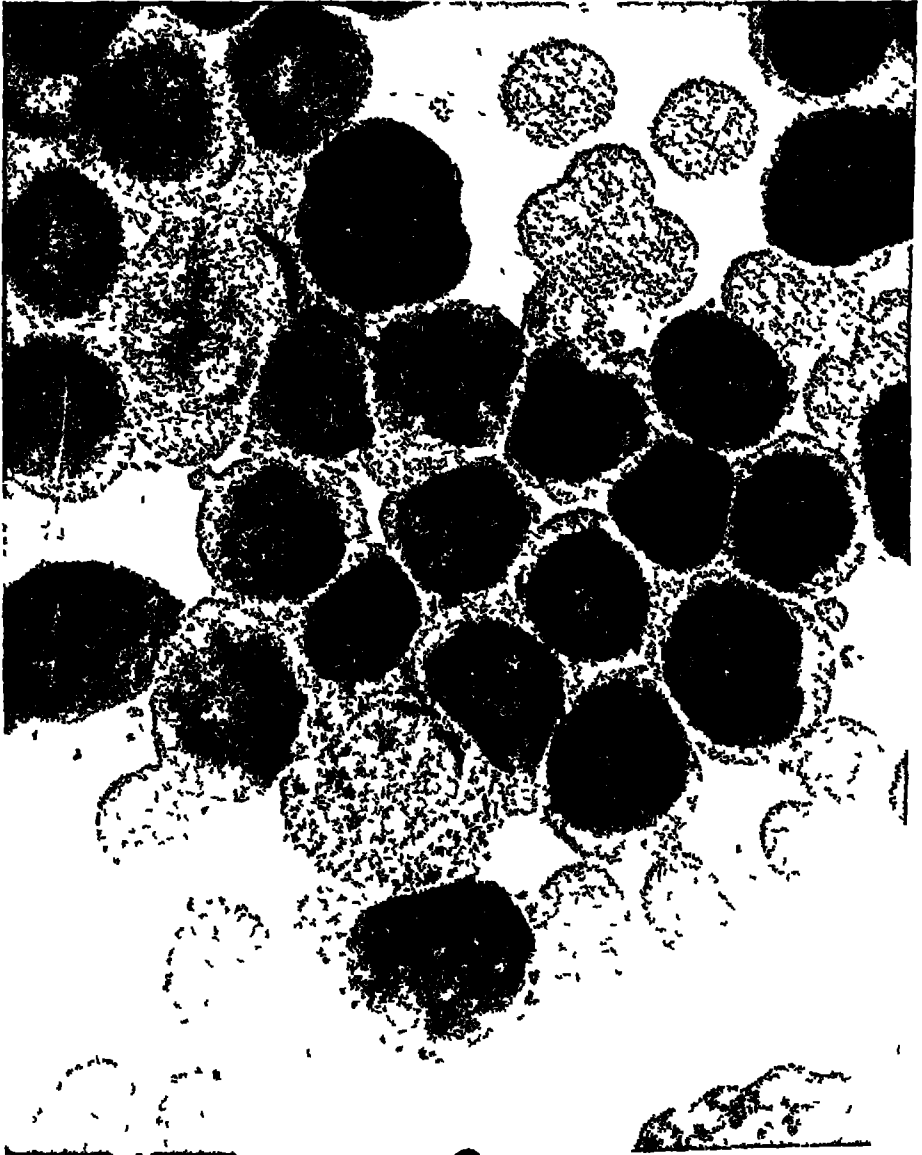


FIG 2 Myeloblastic leukemia. The predominating cells are myeloblasts, a few young myelocytes are present. Aspirated sternal marrow. Wright's stain. $\times 920$

dense, fine, brick-red granulation. In marrow films the cytoplasm of the histiocytes is usually abundant, but in the case of cells obtained from the circulating blood it may be quite scanty and irregular.

Instances of leukemia classified under the several types mentioned have been further subdivided in accordance with quantitative changes of leukemic cells at the time when the patients were first observed. The blood picture

is termed subleukemic when at least 10 per cent of the circulating white cells exhibit a specific type of abnormality on which the morphologic diagnosis is based, but the total of such cells does not exceed 10,000 per cubic millimeter. The condition is considered leukemic when the number of cells exhibiting the type-specific abnormality exceeds 10,000 per cubic millimeter. It is to be emphasized that such a distinction is arbitrary, and that transition from one phase to the other is frequently observed. Nevertheless, separate consideration of instances of subleukemic leukemia is justified for two reasons. First, in the more acute types of leukemia, but not usually in the chronic forms, an unelevated white blood cell count portends, as a rule, a

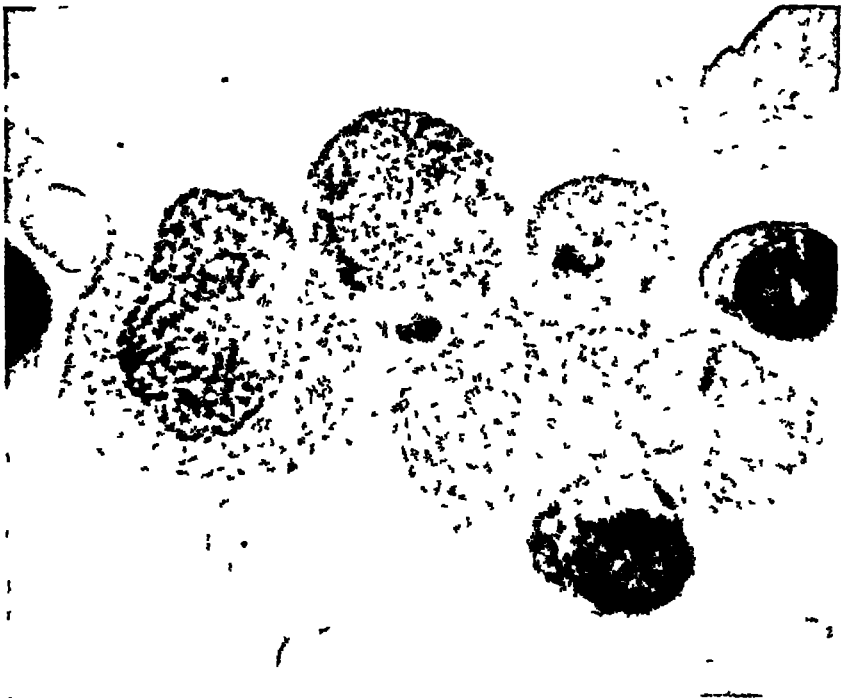


FIG 3 Acute subleukemic histiomonocytic leukemia. The cells are all histioblasts or histiocytes. Aspirated sternal marrow. Wright's stain. $\times 920$.

longer duration of life. Second, it is in the presence of a subleukemic blood picture that an erroneous diagnosis is most likely to occur. Leukopenia, or a leukocyte count within the normal range, is observed least often in the commonest form of leukemia, the myelocytic. Moreover, whereas subleukemia of the lymphogenous or histogenous type is apt to be overlooked, the diagnosis of subleukemic myelogenous leukemia is frequently mistakenly made. Such cases usually represent instances of leukopenic leukemoid reactions in the presence of neoplastic invasion of the marrow, or of miliary tuberculosis, or they fall in the ill-defined group of non-leukemic myeloid metaplasias.^{6, 7}

The difficulties involved in the diagnosis of subleukemic histiomonocytic leukemia, and particularly its differentiation from non-leukemic reticulo-endotheliosis, have been thoroughly discussed by Downey⁴ and by Jaffe⁸ The patient who supplied the data presented on chart 2 was observed by Dr Raphael Isaacs for several years in subleukemic phase before developing leukocytosis⁹ The case is similar to that reported by Derischanoff,¹⁰ who regarded his patient as manifesting generalized non-leukemic reticulum

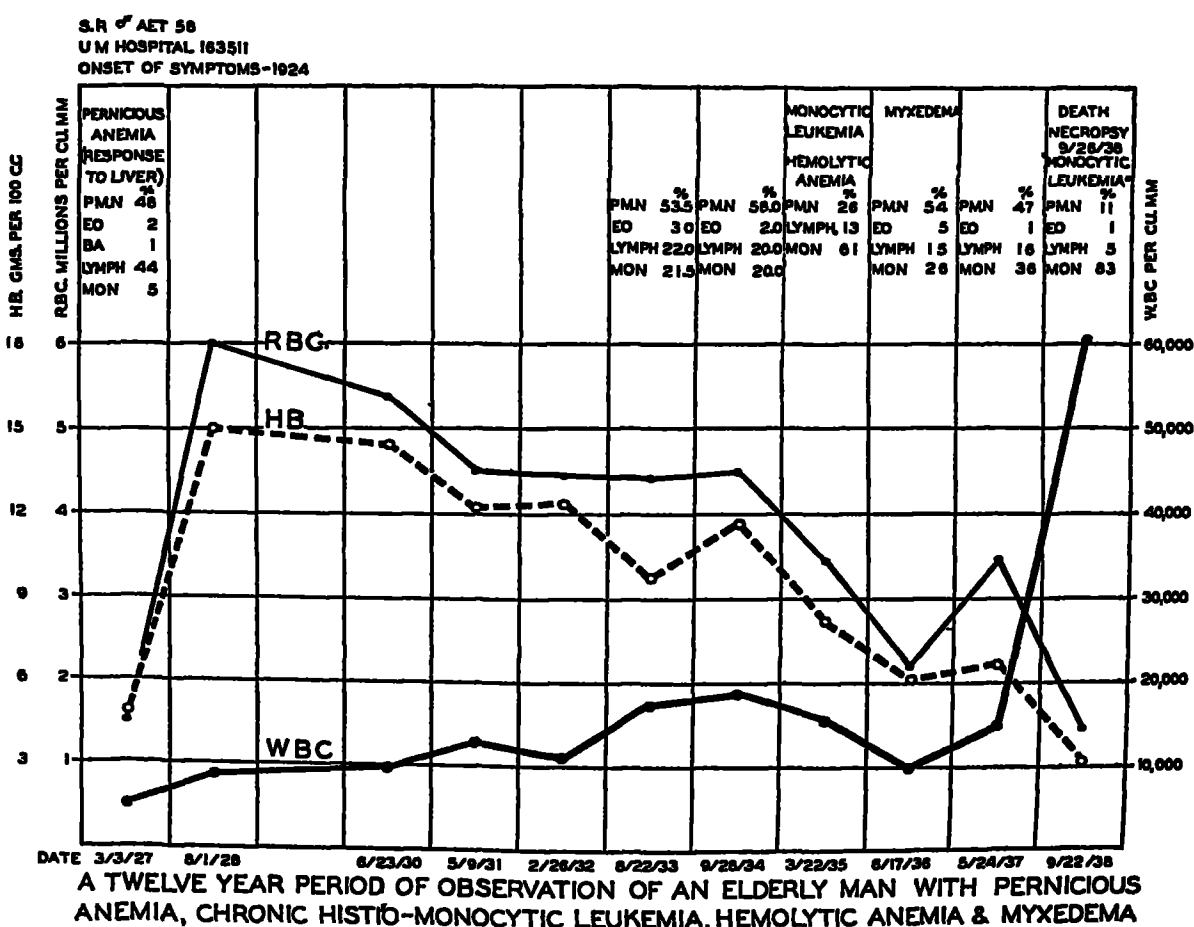


CHART 2

hyperplasia in the presence of Addisonian pernicious anemia Dr Isaacs' patient revealed at necropsy such generalized and characteristic infiltrative changes that to question the leukemic nature of the process would imply more definite criteria for the diagnosis of leukemia than are possessed This case is believed to represent an instance of chronic histiomonocytic leukemia, the existence of which in the non-acute form has been denied by Jaffe⁸ The majority of patients with histiomonocytic leukemia, both subleukemic and leukemic, in the series herein reported, experienced acute illness with early death, although Watkins and Hall report a predominance of the chronic form of the disease in their cases

The age ranges of the patients comprising this series, at the time of onset of their symptoms, are shown on chart 3. Cases of lymphogenous leukemia are excluded since data pertaining to them have been previously reported. After the age of 20, myeloblastic leukemia replaces lymphoblastic as the most common of the acute leukemias. It is believed, in agreement with Wintrobe,¹¹ that little purpose is served by the classification of

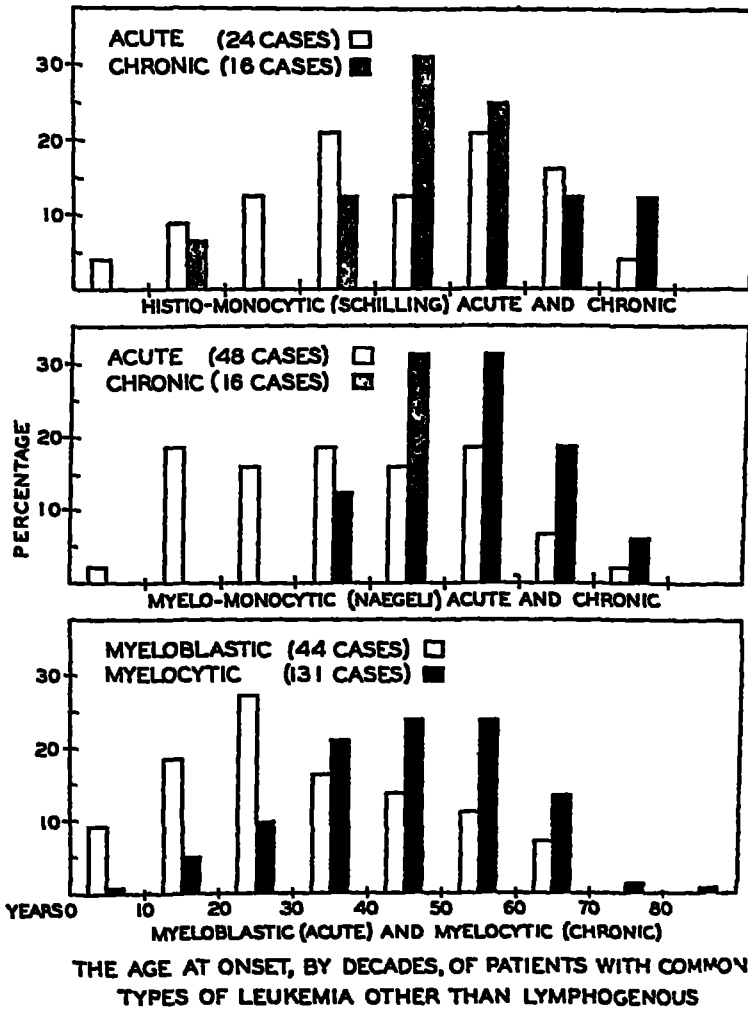


CHART 3

cases of leukemia as subacute, since their resemblance to the acute form is much closer than to the chronic. Among the chronic forms of the disease the myelocytic predominates until the seventh decade is reached when the lymphocytic type is most frequently observed. These findings are in essential agreement with those reported by Ward,¹² Minot and Isaacs,¹³ Minot, Buckman and Isaacs,¹⁴ Leavell,¹⁵ Rosenthal and Harris,⁶ and Wintrobe and Hasenbush.¹⁷ Chronic monocytic leukemia of both myelogenous and

histogenous types, was most often encountered between the ages of 40 and 60, whereas the incidence of the acute forms was more evenly distributed, except at the extremes of life. This age incidence conforms with that of the cases collected by Osgood.¹⁸

Several writers have commented on the apparent increase in the incidence of leukemia, attributing it, usually, to the more widespread use of

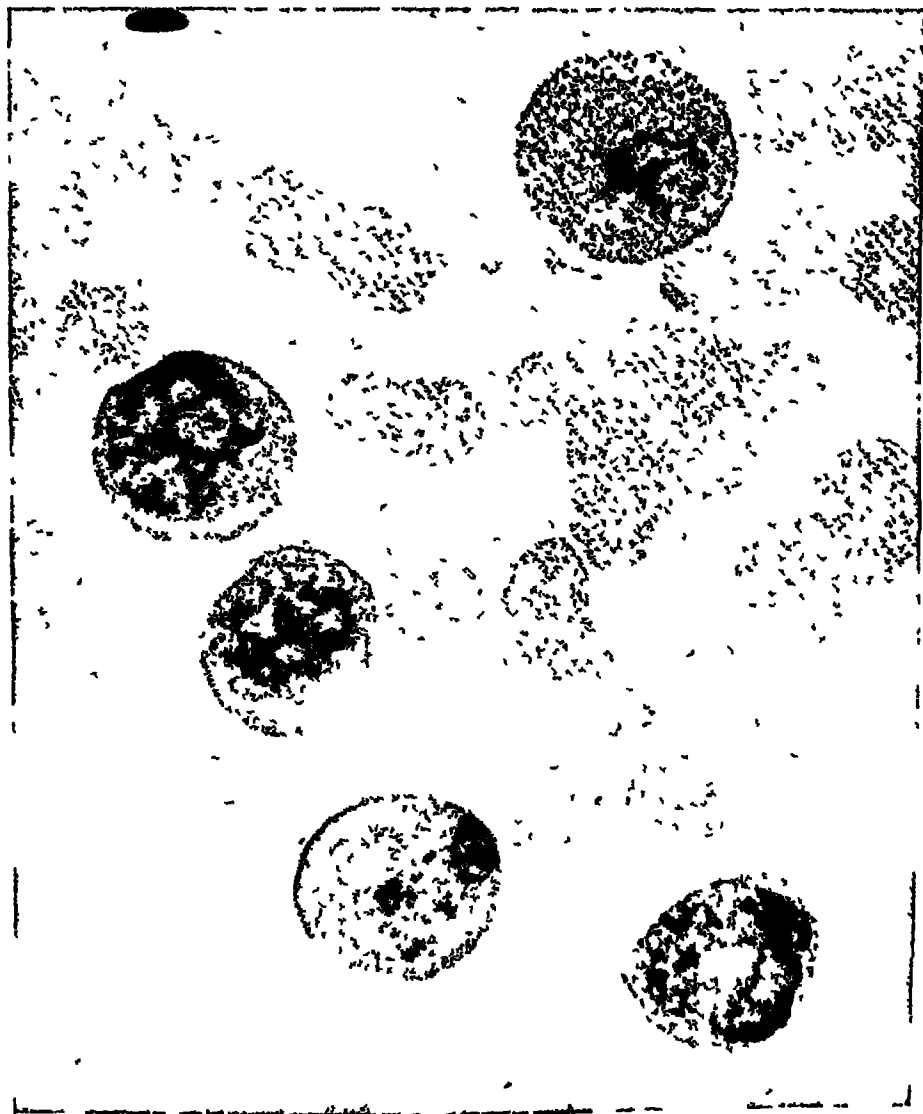


FIG 4 Acute leukemic histiomonocytic leukemia The cells are monocyte types
Blood film Wright's stain $\times 920$

diagnostic laboratory procedures. Lucia,¹⁹ however, believes that the increase is an actual one. With this problem in mind, the patients of this series have been grouped in five year periods according to the date of their first observation at the Simpson Memorial Institute. The periods extend from 1927 to 1941 inclusive (table 1). Comparatively few cases of all types were seen in the year 1927, but taking this fact into consideration, there

TABLE I

The Sex and Median Age and Relative Frequency of the Several Types of Leukemia, and Their Apparent Increasing Incidence

	Per Cent Males	Median Age at Onset (Approx)	Incidence 1927-1931		1932-1936		1937-1941		Total	
			No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
		<i>Years</i>								
Myelocytic	51.9	46	27	20.6	46	35.1	58	44.3	131	26.5
Myeloblastic	68.2	24	6	13.6	14	31.8	24	54.5	44	8.9
Myelomonocytic (chronic)	59.1	51	5	22.7	7	31.8	10	45.5	22	4.4
Myelomonocytic (acute)	52.4	32	3	7.1	12	28.6	27	64.3	42	8.5
Histiomonocytic (chronic)	87.5	45	3	18.8	5	31.2	8	50.0	16	3.2
Histiomonocytic (acute)	62.5	29	2	8.3	7	29.2	15	62.5	24	4.8
Lymphogenous (all types)	—	—	53	24.5	65	30.1	98	45.4	216	43.6
Total	—	—	99	20.0	156	31.5	240	48.5	495	99.9

has been a progressive increase in patients suffering with leukemia in comparison to those on whom diagnoses of other blood disorders have been made. Two reasons which no doubt partially explain this change are evident. Referring physicians, from whom all of our patients are obtained, are diagnosing and treating more patients with various forms of anemia than they did formerly, and at the same time are recognizing and referring cases of leukemia. Few practitioners, however, undertake, without consultation, the management of thrombopenic purpura or hemolytic jaundice, and there has been little or no change in the relative incidence of these diseases throughout the past 15 years. The second possible explanation for the progressive increase in cases diagnosed as leukemia lies in the current use of sternal marrow examination in practically every patient with a suspected primary blood disorder. Undoubtedly, this procedure accounts for the recognition of an appreciable number of cases of subleukemic leukemia but it cannot explain the almost equally great increase in the number of patients with the leukemic forms of the disease. Of special significance is the larger group suffering with acute leukemia, as compared to those with the chronic type, and the more frequent occurrence of the monocytic forms. It seems probable that the increased incidence of chronic leukemia is merely apparent and can be explained by the reasons given above, but on the other hand it is believed that there is an actual increase in acute leukemia.

The results of treatment by roentgen irradiation are shown in table 2. The plan of therapy has involved, in almost all cases, an intensive short course of treatments with exposure limited usually to the splenic area in cases of myelocytic and chronic myelomonocytic leukemia. Two hundred kilovolts and 25 milliamperes are generally used, with distance of 50 cm,

TABLE II

Response to Intensive Short-Course Roentgen Therapy in Cases of Leukemia *

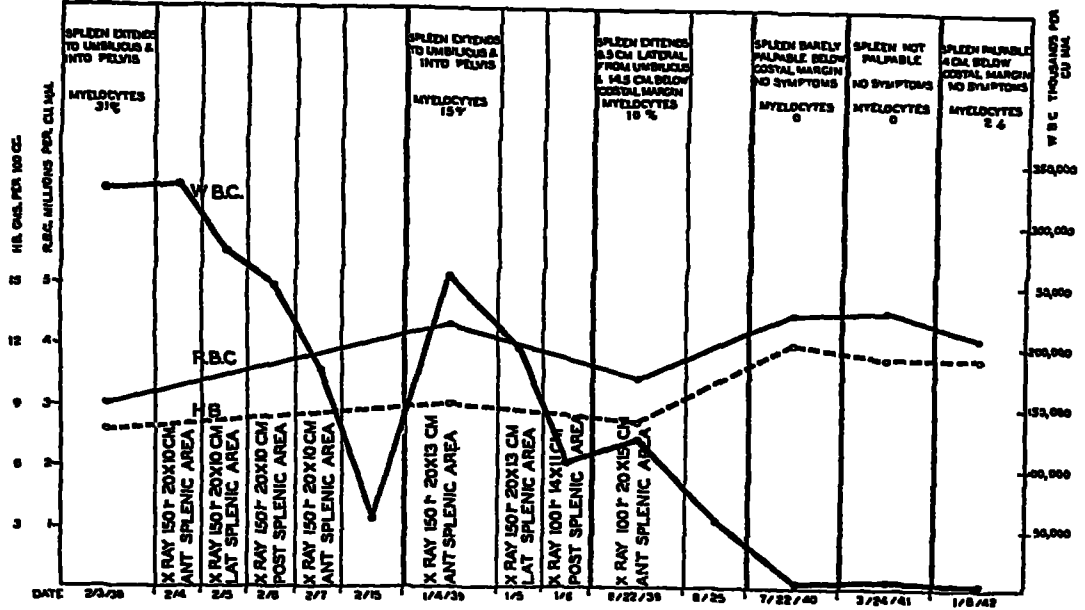
Type of Leukemia	Total Number	Unfavorable		None		Fair		Good		Very Good		Excellent	
		No	%	No	%	No	%	No	%	No	%	No	%
Myelocytic	104	0	0 0	2	1 9	8	7 7	38	36 5	43	41 3	13	12 5
Myeloblastic	16	5	31 3	9	56 3	2	12 5	0	0 0	0	0 0	0	0 0
Myelomonocytic (chronic)	17	0	0 0	5	29 4	5	29 4	5	29 4	2	11 8	0	0 0
Myelomonocytic (acute)	8	3	37 5	4	50 0	1	12 5	0	0 0	0	0 0	0	0 0
Histiomonocytic (chronic)	6	0	0 0	2	33 3	0	0 0	3	50 0	1	16 7	0	0 0
Histiomonocytic (acute)	1	0	0 0	1	100 0	0	0 0	0	0 0	0	0 0	0	0 0
Lymphocytic	50	0	0 0	2	4 0	6	12 0	10	20 0	13	26 0	19	38 0
Lymphosarcoma	52	12	23 1	10	19 2	13	25 0	6	11 5	6	11 5	5	9 6
Cell	10	3	30 0	4	40 0	3	30 0	0	0 0	0	0 0	0	0 0
Lymphoblastic													

* Unfavorable, exacerbation of leukemic process with early death, none, course of disease apparently unaltered, fair, transient clinical improvement but no real remission, good, significant clinical and hematologic improvement lasting three to six months, very good, lasting six to 12 months, excellent, lasting more than 12 months

copper filter, 5 mm, aluminum filter, 1 mm, size of field 10 by 10 to 15 by 20 cm, skin dose 100 to 200 roentgens to each field, with a total of 3 to 5 fields over the anterior, lateral and posterior surfaces of the splenic area. Treatments may be given on consecutive days and in any case are preferably carried out as rapidly as possible (Isaacs²⁰), except that not more than one field is treated during a 24 hour period. It should be emphasized that not all patients will tolerate the maximum treatment outlined above, and that the reaction is often unpredictable. Therefore, at the outset, smaller doses and more limited fields should be employed.

The indications for radiation therapy in myelocytic and myelomonocytic leukemias are symptoms of anemia, of increased metabolism, of pressure from splenomegaly, and of pain in or referred from the splenic area. In the absence of disabling symptoms therapy is deferred. The level of the leukocyte count at the time of institution of treatment bears little relation to the indication for its use, but the rapidity of decline of the white blood cell count is a useful guide to its continued employment. As many observers have pointed out, and as the data here presented indicate, the value of radiation therapy is limited to patients with the chronic forms of leukemia. Best results are obtained in the myelocytic and lymphocytic varieties, but the degree of improvement, the duration of the remission, and the time which will elapse before the occurrence of a refractory state cannot be foreseen in any individual case.

TRACT 34 UM HOSPITAL #47159
ONSET OF SYMPTOMS MAY 1937



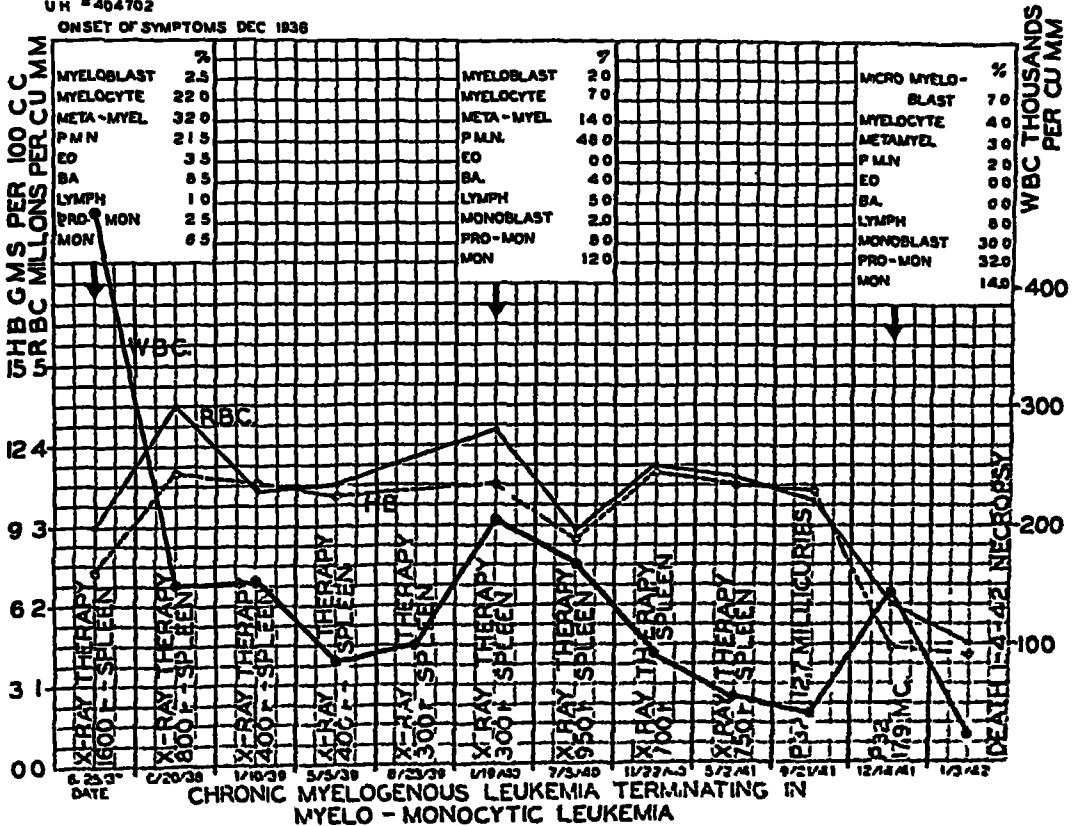
UNUSUALLY GOOD RESPONSE TO ROENTGEN THERAPY EXHIBITED BY A YOUNG WOMAN WITH MYELOCYTIC LEUKEMIA

CHART 4

VW ♀ AET 32

UH #404702

ONSET OF SYMPTOMS DEC 1936



CHRONIC MYELOGENOUS LEUKEMIA TERMINATING IN
MYELO-MONOCYTIC LEUKEMIA

CHART 5

H J & AET 49
U H 432132

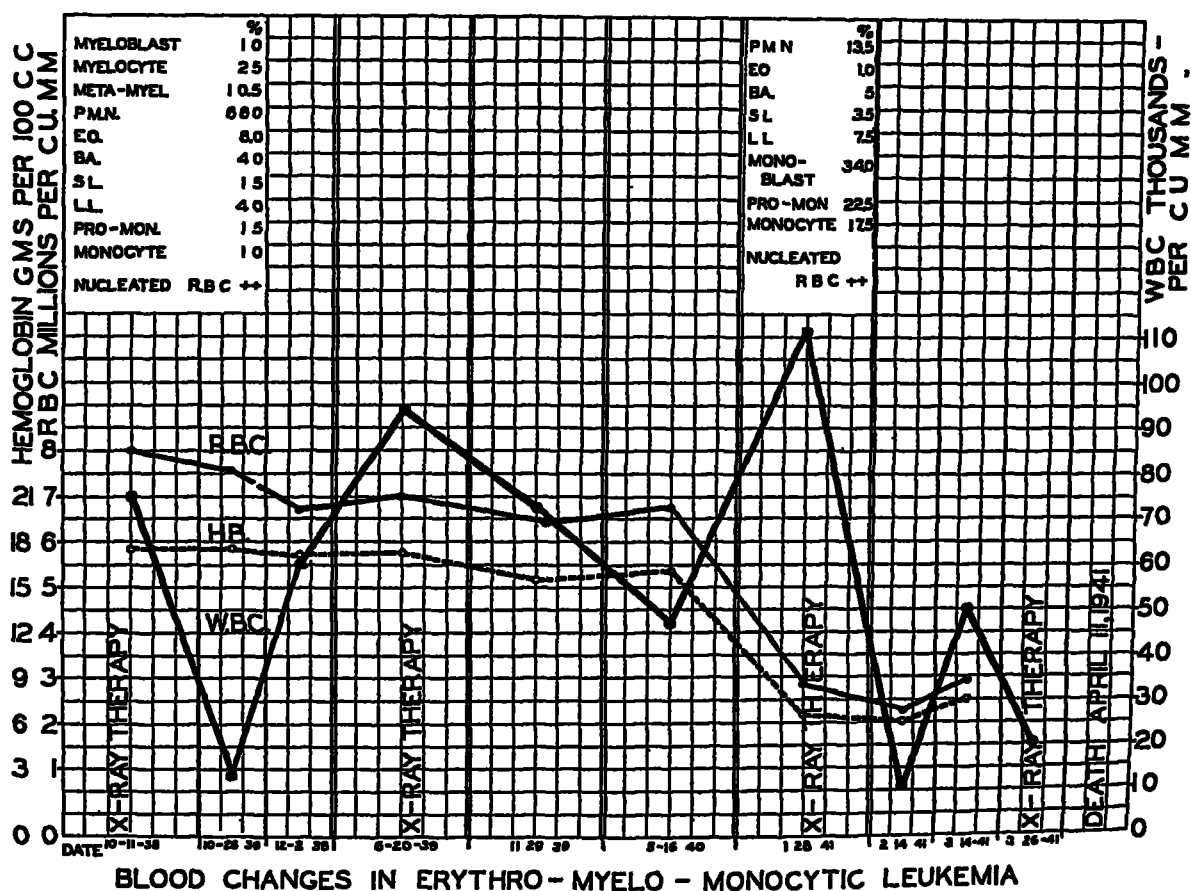


CHART 6

Illustrations of response to radiation therapy are provided by the patients supplying the data shown on charts 4, 5 and 6. In the first instance a remarkably fine result was obtained, and for a period of two years the patient, suffering with myelocytic leukemia, was entirely free from subjective and objective manifestations of the disease. At present, she is symptomatically well, but the presence of myelocytes in the peripheral blood and the slight but demonstrable increase in the size of the spleen indicate the beginning of exacerbation*.

The second patient demonstrates the more usual type of response to radiation, but her case is worthy of special note because it is an instance of transition from the myelocytic to the myelomonocytic type of leukemia, as previously reported by Craciuneaunu and Calalb²¹ and by Hall and Watkins²². Such cases emphasize the close relationship of this form of monocytic leukemia to the myeloblastic developmental series.

The third case is of particular interest. The patient was first seen in 1938 and at that time he exhibited polycythemia with many circulating late

* This patient died on Sept 2, 1942 in an acute subleukemic exacerbation of his disease. The terminal blood values were as follows: RBC 1,400,000 per cu mm, hemoglobin 38 grams per 100 c.c., hematocrit 130 per cent, WBC 500 per cu mm, of which practically all were myeloblasts. No roentgen therapy had been given since August, 1939.

normoblasts, and a myelocytic leukemia type of leukocyte picture. Sternal aspiration revealed an extremely cellular marrow with active, but not apparently abnormal, erythropoiesis and granulopoiesis. Although, on re-examination of these films, monocyte developmental forms could be identified, at the time of the initial study they were not sufficiently conspicuous to occasion special note. A good result was obtained from radiation therapy, but when the patient returned in 1941, after an interval of eight months, a



FIG 5 Myelocytic leukemia terminating in myelo-monocytic leukemia (patient V W, chart 5). From above down the cells are, respectively, a myeloblast, a monocyte, and a promonocyte. Blood film Wright's stain $\times 920$

great change was noted both in the peripheral blood and marrow. Anemia was severe, and the leukocytes were predominantly of the monocyte series with 34 per cent in the blast stage of development. The marrow did not reveal displacement of erythrocyte forming tissue, but instead proliferation of early basophilic erythroblasts with very little evidence of maturation. These cells did not resemble megaloblasts, but possessed many of the features of the marrow cells seen in cases of Cooley's anemia. Concurrently there were observed, in separate groups, all stages of monocyte development with mitotic figures fairly common. Typical myeloblasts and myelocytes were

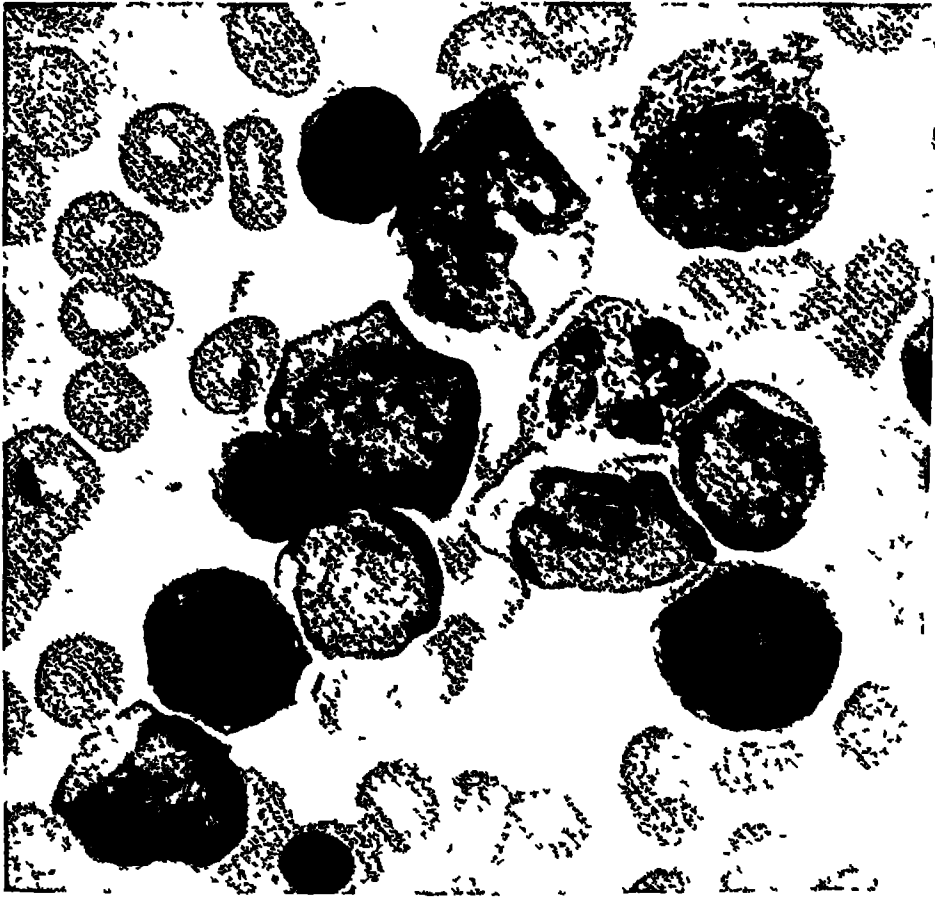


FIG 6 Erythro-myelo-monocytic leukemia (patient H S, chart 6) The cell at upper right is a histiocyte, probably not directly involved in the leukemic process. Below it is a neutrophil. The cells with darker nuclei are members of the erythrocyte series. The others are all developmental forms of the monocyte. Aspirated sternal marrow. Wright's stain. $\times 920$

almost absent. Unfortunately, this man died at home, after failing to benefit from roentgen therapy, and necropsy was not obtained.

CONCLUSIONS

A series of 495 cases of leukemia is reported with respect to the sex and age incidence and the relative frequency of the various types.

Particular emphasis is placed on the differentiation of monocytic leukemia related to the myeloblast and that form believed to arise from an undifferentiated reticulum cell or histioblast.

The relative and absolute increase in the acute forms of leukemia observed in recent years is believed to indicate a greater incidence of such diseases.

Roentgen therapy of leukemia is discussed and the results of such treatment are presented.

Hematologic data on four illustrative cases of leukemia are reported.

BIBLIOGRAPHY

- 1 BETHELL, F H Lymphogenous (lymphatic) leukemia diagnostic, prognostic and therapeutic considerations based on an analysis of its morphologic and clinical variants, Jr Am Med Assoc, 1942, cxviii, 95
- 2 NÄGELI, OTTO Blutkrankheiten und Blutdiagnostik, Ed 5, 1931, Julius Springer, Berlin
- 3 RICHTER, M N Leucemia In DOWNEY, HAL Handbook of hematology, 1938, Paul B Hoeber, Inc, New York, Vol IV, p 2887
- 4 DOWNEY, HAL Monocytic leucemia and leucemic reticulo-endotheliosis, Ibid, Vol II, p 1275
- 5 WATKINS, C H, and HALL, B E Monocytic leukemia of the Naegeli and Schilling types, Am Jr Clin Path, 1940, x, 387
- 6 JACKSON, H, JR, PARKER, F, JR, and LEMON, H M Agnogenic myeloid metaplasia of spleen, syndrome simulating other more definite hematologic disorders, New England Jr Med, 1940, ccxxxii, 985
- 7 REICH, C, and RUMSEY, W, JR Agnogenic myeloid metaplasia of the spleen, Jr Am Med Assoc, 1942, cxviii, 1200
- 8 JAFFE, R H The reticulo-endothelial system In DOWNEY, HAL Handbook of hematology, 1938, Paul B Hoeber, Inc, New York, Vol II, p 977
- 9 ISAACS, R, and STURGIS, C C Types of monocytic leukemia, Trans Assoc Am Phys, 1936, li, 40
- 10 DERISCHANOFF, S M Ueber die Systemhyperplasien des Reticulo-Endothel, Frankfurt Ztschr f Path, 1931, xli, 184
- 11 WINTROBE, M M Clinical hematology, 1942, Lea and Febiger, Philadelphia
- 12 WARD, G The infective theory of acute leukemia, Brit Jr Child Dis, 1917, xiv, 10
- 13 MINOT, G R, and ISAACS, R Lymphatic leukemia age incidence, duration and benefit derived from irradiation, Boston Med and Surg Jr, 1924, cxc, 1
- 14 MINOT, G R, BUCKMAN, T E, and ISAACS, R Chronic myelogenous leukemia age incidence, duration, and benefit derived from irradiation, Jr Am Med Assoc, 1924, lxxxi, 1489
- 15 LEAVELL, B S Chronic leukemia A study of the incidence and factors influencing the duration of life, Am Jr Med Sci, 1938, cxci, 329
- 16 ROSENTHAL N, and HARRIS, W Leukemia its diagnosis and treatment, Jr Am Med Assoc, 1935, civ, 702
- 17 WINTROBE, M M, and HASENBUSH, L L Chronic leukemia the early phase of chronic leukemia, the results of treatment and the effects of complicating infections, a study of eighty-six adults, Arch Int Med, 1939, lxix, 701
- 18 OSGOOD, E E Monocytic leukemia report of six cases and review of one hundred and twenty-seven cases, Arch Int Med, 1937, lxv, 931
- 19 LUCIA, S P Leukemia evaluation of the therapy, California and Western Med 1941, v, 119
- 20 ISAACS, R The relation of cell types in leukemia to sensitivity to radiation Folra haemat, 1934, lii, 414
- 21 CRACIUN-PAUNU, A, and CAIALB G Poussée monocytique au cours d'une leucémie myéloïde chronique accompagnée d'hypertrophies ganglionnaires, Sang, 1931, v, 397
- 22 HALL, B E, and WATKINS C H Myelogenous leukemia changing to monocytic leukemia, report of case, Am Jr Clin Path, 1941, vi, 443

EXPERIMENTAL STUDIES ON HEPARIN AND ITS INFLUENCE ON TOXICITY OF DIGITALOIDS, CONGO RED, COBRA VENOM AND OTHER DRUGS *

By DAVID I. MACHT,† M D , F A C P , *Baltimore, Maryland*

INTRODUCTION

AT first engaging the attention primarily of physiologists and hematologists, the study ^{1, 2, 3} of heparin was soon taken up also by biochemists, who of recent years have succeeded largely in unraveling its complicated chemical structure. More recently, heparin has acquired a practical significance through the work of clinical investigators who discerned its potentialities as a therapeutic agent. Indeed, Howell and McDonald ⁴ had suggested such clinical applications of heparin, but its actual value in medical practice was not demonstrated until the painstaking investigations of American, Canadian and Swedish scientists were well under way. It is far beyond the scope and aim of this paper to cite the complete literature, which may be gleaned from Jorpes' excellent monograph ⁵ and Mason's comprehensive review ⁶ of the subject. Clinically heparin has been advocated especially as a prophylactic agent against thrombo-embolic complications of various kinds. Among the earlier contributions to the subject may be mentioned the work of Crafoord ^{7, 8} and the brilliant experimental research on animals as well as clinical contributions of Murray, Jaques, Perrett, Best ^{9, 10} and Solandt ¹¹. This work demonstrated the usefulness of heparin in preventing the formation of clots in blood vessels in animals as well as the smaller incidence of thrombo-embolic complications in postoperative treatment of human patients. More recent clinical papers on the subject have been published by Crafoord, Jorpes and Best ^{12, 13, 14}. Leissner ¹⁵ used heparin in obstetric practice for preventing thrombosis and Clason ¹⁶ reports the results obtained with this drug in three cases of pulmonary embolism. In the ophthalmological field prevention of thrombosis in retinal veins has been reported by Ploman, ¹⁷ Holmin, ¹⁸ Bostrom and William-Olsson ¹⁹ and, more recently, by Ferguson ²⁰. An attempt to combine heparin with various chemotherapeutic agents in the treatment of bacterial endocarditis has been described by Kelson, ²¹ and more recently by a group of clinicians in Boston ²². No longer now of merely physiological and biochemical interest, heparin merits a place with the newer pharmacotherapeutic agents. A comprehensive pharmacological study of this substance was, therefore, deemed desirable.

* Received for publication December 22, 1942.

Read before the Section on Pathology and Physiology of the American Medical Association at Atlantic City, June 11, 1942.

† Director, Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc., Baltimore, Maryland.

and in the following pages the writer purposes to report new experimental observations on the subject

Chemistry of Heparin Although not yet completely solved, the chemistry of heparin is now pretty well known, thanks to the work of numerous investigators and especially of Charles and Scott,²³ Bergstrom, Jorpes and Wilander,²⁴ and Chargaff.²⁵ Heparin is a mucitin polysulfuric acid with not less than 40 per cent of sulfuric acid. Being a polysaccharide, it possesses an extremely high negative electric charge, which is probably responsible largely for its reaction with other compounds playing a rôle in the coagulation system. In fact, heparin may be regarded as a sort of hormone regulating the blood coagulation and like the hormones it is produced by a special kind of cell, i.e., the so-called mast cells of the connective tissue, found mainly in vicinity of capillaries and blood vessel walls. Heparin is thought to pass from these cells either directly or by diffusion into the blood stream. The so-called metachromatic granules of these cells, consisting of heparin, exhibit characteristic staining reactions.²⁶

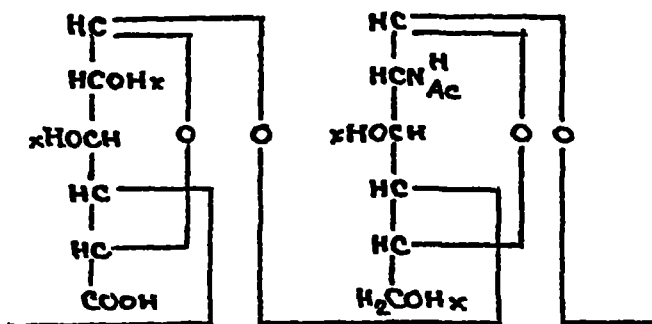


FIG 1 The organic moiety of heparin, mucitin = glucuronic acid + acetylated glucosamine

The heparin employed in the present experiments was prepared in our chemical research laboratory. As a matter of historical record, it may be stated here that this was the first chemical research laboratory to produce heparin for Professor William H. Howell, who 20 years ago entrusted Dr. H. A. B. Dunning with its preparation for his later experiments. Since then our manufacture of heparin for research purposes and in a more highly purified form has been continuous. Originally extracted by us almost exclusively from dog livers, heparin in recent years through improvements in technic has been made not only from livers but also from other organs.* The heparin is assayed in this laboratory by Howell's original method on freshly drawn cat's blood, and its physiological antithromboplastic activity is expressed in terms of the number of cubic centimeters of blood which the addition of one milligram of the drug will keep fluid for 24 hours under standardized conditions. Specimens of heparin with a potency as high as

* Due acknowledgment is hereby made of the hearty coöperation in this investigation of our research chemists, Drs. Fitzgerald Dunning, Charles A. Dunning and Wilton C. Hardin, and Mr. Arthur E. Stickel.

1 200 have thus been prepared, but it has been found for economical reasons and for all practical experimental purposes that a purified heparin of a potency of 1 50 is quite satisfactory for physiological and pharmacological research In fact, for a great many routine procedures employed in the clinical laboratories less expensive weaker preparations of heparin (with a potency of 1 75 or 1 10) have been found entirely adequate

Influence of Heparin on Toxicity of Ouabain The powerful cardiac tonic ouabain is generally assayed by determining its lethal dose for cats A definite concentration is prepared by dissolving a given weight of the glucoside in physiological salt solution and at regular intervals this saline is injected into the femoral vein of a cat under light anesthesia until the heart stops, the respiration continuing for a brief interval thereafter Such

TABLE I
Assay of Ouabain Solution, 1 100,000

M L D of Ouabain Alone	M L D of Ouabain Preceded by Heparin
c.c. per kilo	c.c. per kilo
8 8	11 0
9 8	13 0
9 0	14 0
10 0	15 0
9 0	15 0
8 8	14 0
8 2	20 0
15 5	20 7
10 5	16 5
10 0	12 3
10 5	10 7
11 4	15 6
8 7	11 4
8 5	11 4
9 2	10 3
Average, 9 9 c c per kilo	Average, 14 1 c c per kilo
P E —0 32	P E —0 56
σ —1 74	σ —1 03
Critical Ratio—6 5	P E —0 32
P E —0 32	P E —0 56

assays are frequent in this laboratory, the concentration of ouabain employed being usually 1 100,000 by weight When a specimen of ouabain was thus assayed on two series of animals, one of each pair being heparinized 5 to 10 minutes before injection of the drug while the other was employed as usual, the lethal dose for the heparinized cats was generally greater than that obtained from normal control cats Statistical analysis of the data derived from such sets of experiments demonstrated the validity of difference in the m l d obtained in the two series Table 1 shows the difference in the m l d of ouabain required for heparinized and non-heparinized cats, respectively A comparison of the average lethal doses in the two sets reveals that the critical ratio is 6 5, which is far above that required for a valid difference according to statistical criteria

Influence of Heparin on Toxicity of Digitalis Results similar to those obtained with ouabain were derived from experiments with tinctures of digitalis. Dilutions of digitalis tincture with physiological saline 1:10 were assayed on heparinized and control cats by the Brodie-Hatcher method. The experiments with digitalis and those with ouabain were generally performed in pairs, i.e., one on a normal cat and another on a cat previously heparinized to eliminate variables affecting the toxicity of the digitalis glucosides as, for instance, sudden changes in barometric pressure and other meteorological conditions found to influence the potency in these two sets of cats.²⁷ Thus in a series of 50 cats, the average lethal dose for the controls was 8.5 cc, whereas that for the heparinized animals was 10.2 cc. In control readings σ was 2.63 and P.E., ± 0.35 , and for readings obtained from heparinized animals σ was 2.68 and P.E., ± 0.36 . The P.E. difference between the two series was 0.5 and the critical ratio, 3.4, indicating a statistically significant difference between the results derived from both.

Coagulation Studies on Digitaloid Drugs To analyze these differences in m.l.d. of ouabain and digitalis for heparinized and non-heparinized animals, studies were made on the coagulation of blood *in vitro* and *in vivo*. Samples of blood were obtained from cats under light anesthesia at the beginning of digitalis or ouabain assay and other specimens were drawn from the carotid artery at regular intervals during its progress. It was found that coagulation time of whole blood studied by Howell's method was progressively shortened from beginning to end of the experiment. Similar results were obtained with ouabain. See the subjoined protocols.

Effect of Digitalis Injections in Vivo on Coagulation of Blood

(Experiment of Nov. 28, 1941, on cat 3.6 kilo, under ether) Assay of 1:10 Dilution of Digitalis. Total injected, 24 cc, M.L.D., 6.6 cc per kilo

	Coagulation Time
Normal	8 minutes
After injecting 6 cc	6 minutes, 30 seconds
After injecting 10 cc	5 minutes, 15 seconds
After injecting 15 cc	3 minutes, 45 seconds
After injecting 20 cc	1 minute, 45 seconds
After injecting 23 cc	1 minute, 15 seconds

Effect of Ouabain Injections in Vivo on Coagulation of Blood

(Experiment of Dec. 19, 1941 on cat 2.38 kilo, under ether) Assay of Ouabain Sol., 1:100,000—Total injected, 25.5 cc, M.L.D., 0.106 mg per kilo

	Coagulation Time
Normal	9 minutes, 30 seconds
After injecting 10 cc	4 minutes
After injecting 15 cc	2 minutes, 40 seconds
After injecting 20 cc	1 minute, 40 seconds

A more extensive study was then made of the effect of various digitaloid glucosides on coagulation of shed blood *in vitro*. Small samples of blood

were mixed with solutions of the different glucosides in varying concentration and their coagulation time was determined. The entire series comprised specimens of digitalin (3), digitalein, digitoxin, digitonin, digitanid, strophanthin (3), ouabain, convallamarin, scillaren and bufagin, the digitaloid principle obtained by Abel and Macht²⁸ from the toad, *Bufo aqua*. All these principles were found definitely to hasten coagulation of blood in vitro.

Control experiments were made with a long series of potent pharmacological agents comprising the glucosides esculin, salicin and phloridzin, the salts of the alkaloids atropine, homatropine and physostigmin, quinine, HCl, quinidine, epinephrine HCl, ephedrine, morphine, codeine, cocaine, spartein, aconitine, crystalline sex hormones, sulfanilamide and other sulfa drugs. The effect of most of these drugs on the coagulation of blood was insignificant. The chief exceptions were epinephrine and crystalline progesterone, both of which tend to shorten coagulation time. The thromboplastic properties of digitaloid drugs are not due to a hemolytic effect because with the exception of two samples of digitalin and of digitonin (a saponin), none produced any hemolysis. The difference in toxicity of digitalis and ouabain for heparinized and control cats can perhaps be ascribed to the thromboplastic properties of the digitaloid principles. To support this view histological studies are being made on hearts of cats used in such tests in hope of detecting microscopic evidence of intravascular clotting.

Experiments with Congo Red Congo red has long been known as a laboratory reagent for detecting free hydrochloric acid, as a test stain for amyloid and for the estimation of the functional state of the reticulo-endothelial system²⁹. Moreover in recent years its use has been extended to therapeutic procedures, and it has been employed empirically with little scientific basis in the treatment of pernicious anemia,³⁰ pulmonary tuberculosis,³¹ purpura hemorrhagica and other conditions. One writer has even recommended it as a chemotherapeutic agent in certain forms of streptococcus septicemia³². Serious untoward reactions have occasionally been reported after intravenous use of this drug. Macht, Harden and Grumbein³³ accordingly made a toxicological study of this subject and found that commercial samples of congo red varied much in toxicity and that it was necessary to use a reliably standardized sample for intravenous injection. They found also that the toxicity of this drug for cats was lessened by previous heparinization of the animals. Could this decrease in toxicity be correlated with the effects of congo red on coagulation of the blood? Taliaferro and Haag, who have published an excellent pharmacological study of the dye, reported that injections of small doses of congo red rapidly diminished the coagulation of the blood but when large doses were administered the converse effect was produced and a marked delay in coagulation time was noted³⁴. Macht, Harden and Grumbein made similar observations in studies on coagulation of cat's blood in vitro, but Richardson³⁵ noted no hastening of coagulation after small doses in rabbits. The

results of additional experiments on the toxicity of congo red which the writer made in connection with the present study confirmed his findings. Coagulation time of whole blood obtained from non-heparinized cats during course of administration of congo red was definitely *lessened* after *small injections* but markedly prolonged after large doses. This is illustrated by the following protocol

Coagulation Experiment No 1 with Congo Red on Cat Weighing 1.5 Kilo

	Coagulation Time
Normal	7 minutes
After injecting 10 mg of congo red	4 minutes, 45 seconds
After injecting 10 more mg of congo red	5 minutes
After injecting 50 mg of congo red	30 minutes
After injecting 100 mg of congo red	35 minutes
After injecting 150 mg of congo red	over one hour

Influence of Heparin on Toxicity of Cobra Venom Recently introduced into medical practice as a therapeutic agent for the relief of pain, cobra venom is now being used as a substitute for the opiates and other powerful analgesics^{86, 87, 88}. Various investigators have, therefore, made extensive toxicological studies of this drug. The principal constituent of cobra venom and that responsible for its analgesic action is a neurotoxin, the chemistry of which is still not completely known, but the latest research on the subject suggests that the cobra neurotoxin is probably of a glucosidal nature⁸⁹. In addition to this active principle, crude cobra venom contains various hemotoxins such as hemolysins, coagulants, agglutinins and precipitins. In general the toxicity of crude cobra venom solutions has proved to be greater than that of solutions of cobra venom, from which proteins and hemotoxins had been removed. The present writer investigated the toxicity of crude cobra venom solutions for cats in conjunction with simultaneous administration of heparin. The average lethal dose of solutions of various lots of cobra venom was first determined on control animals. The same solutions were then assayed on other cats receiving from 5 to 10 mg of heparin 10 to 15 minutes before injection of cobra venom was begun. In the majority of such experiments prior heparinization of the cats diminished toxicity of the venom. The subjoined kymographic tracings, recording the respiratory movements of two cats treated in this way, illustrate the results obtained. It will be seen that the lethal dose for the control cat was 58.3 cc per kilo, whereas that for the cat receiving heparin before injection of cobra venom was 86 cc per kilo. Here also, coagulation time varied with the amount of the drug injected.

Anaphylactic Experiments The effect of heparin on coagulation of blood is not its only interesting physiological property. Other systems affected by heparin than those involved in coagulation have been discovered. Among the most important is the relation of heparin to anaphylactic shock. Divergent reports have been made on the subject. Kyes and Strauser⁹⁰ found that heparin injections protected pigeons from shock, and Williams

and Van de Carr ⁴¹ reported similar findings in guinea pigs sensitized with horse serum. A preliminary announcement in 1928 by Macht, Dunning and Stickel ⁴² also described the protective action of heparin against the shock produced by horse serum in sensitized guinea pigs, rabbits and rats. Hanzlik, ⁴³ Reed and Lamson ⁴⁴ did not confirm these findings. Repeating his earlier work, the present writer has recently found that guinea pigs can be protected in varying degrees against the anaphylactic shock contingent upon sensitization to horse serum by prior injections of heparin. Table 2 shows the results obtained in such experiments with 50 guinea pigs, 25 heparinized and 25 used as controls. Prior administration of 5 to 10 mg of heparin solution (1:80) definitely diminished the violence of anaphylactic shock and in some cases prevented such attacks altogether whereas the majority of the controls had severe reactions and died. This corroborative evidence leaves no room for doubt concerning the correlation of heparin effect and anaphylactic shock, at least in some of the lower animals. It was noted that to achieve an antagonizing effect an interval of about 10 minutes must elapse before injection of the antigen. Simultaneous injection of heparin with serum is ineffectual. Closely related to these findings although qualitatively different, are those of other investigators with injections of Witte's peptone in dogs. Wilander ⁴⁵ found that injections of peptone into the circulation of dogs produced a very severe shock with loss in clotting capacity of blood, and this deficiency, it was assumed, was caused by flooding the blood stream with heparin. Wilander's earlier findings have recently been confirmed by Jaques and Waters, ⁴⁶ who showed that the anticoagulating substance in blood of dogs in anaphylactic shock is heparin and isolated it in crystalline form from the blood of such animals.

TABLE II
Anaphylaxis in Guinea Pigs

All Animals Sensitized with 0.5 to 1.0 c.c. of Horse Serum Tests Made Two Weeks Later

Control Guinea Pigs Injected with horse serum alone	Heparinized Animals Injected with 5 to 10 mg of heparin 10 minutes before horse serum was given
19 animals—immediate shock, convulsions and death	8 animals developed mild reactions
6 animals developed severe shock but survived	5 animals developed severe reactions (after 10 to 30 minutes) and died
	2 developed severe shock and died because serum was injected immediately after heparin
	10 animals developed no reaction and remained well
— 25—total	— 25—total

Experiments with Trypsin and Pepsin In connection with the experiences of various investigators with heparin in relation to anaphylaxis, the experiments of Rocha e Silva and Dragstedt ⁴⁷ with trypsin deserve special mention. These authors reported a relation between the liberation of

heparin and administration of trypsin More recently, these authors together with Wells⁴⁸ reported before the Federation of the American Society for Experimental Biology in Boston some further experiences along these lines They found that injections of trypsin solutions in lightly anesthetized rats are rapidly fatal but that administration of heparin will protect such animals from lethal doses of this drug The present writer has been conducting similar experiments on guinea pigs and his findings corroborate completely these observations made on rats A solution of trypsin in physiological saline was injected into the circulation of guinea pigs and the minimal lethal dosage for the animals was determined The following protocol is a good illustration of such an effect

Trypsin Experiment of March 25, 1942

Guinea Pig 1, weighing 700 gm, slowly injected intravenously with 5 c c of trypsin, 25 per cent, in saline

Died in 35 minutes

Guinea Pig 2, weighing 600 gm, injected with 10 mg of heparin (1 100)

Ten minutes later injected with 5 c c of trypsin, 25 c c in saline

Animal depressed but recovered and lived

Inasmuch as another proteolytic enzyme, papain, one of vegetable origin, has been described in the older literature⁴⁹ as being very toxic on injection in animals and producing anaphylactic shock, other experiments were undertaken by the writer with heparin and papain injections of mice This investigation is still in progress but the results already in hand seem to point to an antidotal property of heparin against the toxic action of papain, not unlike that encountered in the research with trypsin Prior injection of heparin into the circulation of mice protected them against lethal doses of the enzyme as may be seen from the following protocol

Papain Experiment of April 1, 1942

A Five mice with average wt of 24 gm, injected in tail vein with 0.5 c c of papain solution, 2 per cent Three out of five mice died within five hours

B Five mice with average wt of 24 gm, injected in tail vein with 5 mg of heparin, 1 50

Each injected 10 minutes later with 0.5 c c of papain solution

One mouse died, and four survived

General Pharmacology Even the experiments of earlier workers employing crude heparin revealed its low toxicity At that time a depressant action was found to be exerted chiefly on the blood pressure which fell considerably after injections of the drug into experimental animals This effect was due to histamine and other impurities mixed with the heparin of that day for later studies with purer products of the drug showed that it was not toxic for the circulatory apparatus with the occasional exception of the blood Sporadic clinical cases of pathological bleeding have been reported after administration of heparin for therapeutic use Thus Ershler and

Blaisdell⁵⁰ describe hematuria after use of heparin in thrombosis of the cavernous sinus. To the same category belong the recent laboratory findings of Copley and Lalich,⁵¹ who described a hemophilia-like condition in mice after repeated enormous doses of heparin. Strangely enough, these investigators state that the condition they describe was not produced by all brands of heparin they used. Although hemorrhagic tendencies may occur occasionally in patients receiving heparin treatment, such a complication is conspicuous by its rarity,⁵² because of the rapid dissipation of the drug's effect after its introduction into the body. Indeed this circumstance is the principal obstacle to the practical application of heparin in the clinic. In this respect heparin contrasts strikingly with some of the newer anticoagulants described in recent medical literature.⁵³ Yet because of these incidental untoward reactions observed after clinical use of heparin the author decided to study anew its toxicology, especially after administration of large doses of the highly purified product. Experiments were made on the action of heparin on the circulation, the respiration, kidney and liver function, and on the central nervous and neuromuscular systems of cats and rabbits. It was established that the drug affected none either in acute experiments or in animals kept under observation for longer intervals. Figure 3, illustrating the results obtained in such studies on circulation and respiration, shows the effect of a rapid injection of 150 mg of heparin (1:80) into the femoral vein of an anesthetized cat. Although the amount of heparin injected in such animals was sufficient to keep 12,000 c.c. of cat's blood fluid for 24 hours *in vitro*, no depressant effect was noted on the respiration and circulation. In fact, other experiments revealed that injections of large doses of heparin occasionally stimulated the vasomotor apparatus, as a small and sustained rise in blood pressure indicated.

Studies conducted on rabbits by the phenolsulphonphthalein method revealed that such large doses of heparin did not impair the kidney function.

The bromsulphalein test also yielded completely negative findings in studies on the liver function of rabbits.

Equally interesting were the results of an investigation of the effect of heparin on the central nervous system and neuromuscular apparatus. Employing a technique used in other researches,^{54, 55} the writer studied the behavior of albino rats trained to run in a circular maze after injections of heparin ranging from 1 to 20 mg. had been made in such animals by the intramuscular, intraperitoneal and intravenous routes. It was found that in no case was any depression of the central nervous system or disturbance of neuromuscular coordination produced. Analyses of the numerous data derived from such experiments revealed, on the contrary, a slightly stimulating effect on the running time and behavior of the rats. All the foregoing findings with regard to circulation, respiration, kidney and liver function and the effects of heparin on the central nervous and neuromuscular apparatus speak for a wide margin of safety for this drug.

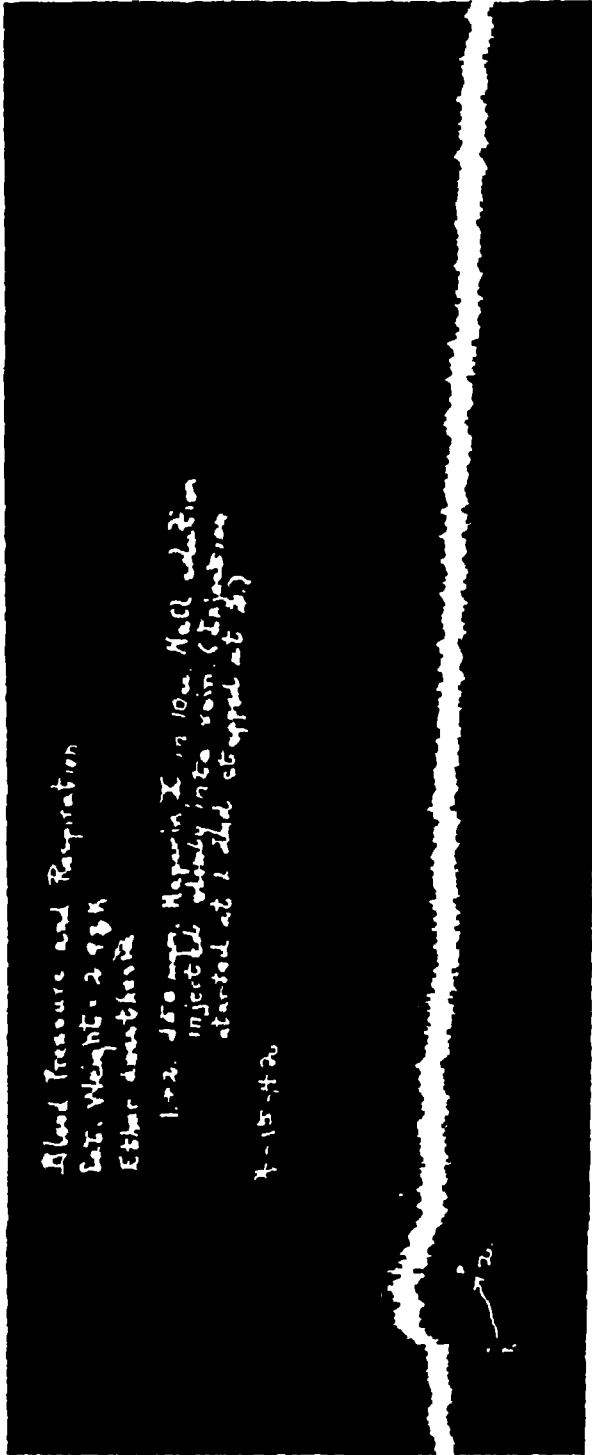


FIG 3 Cat 29 kilo—ether anesthesia Blood pressure and respiratory tracings after 150 mg of heparin

Phytopharmacological Studies The writer has discovered a new property of heparin which is of more general biological interest. It has been the custom in this laboratory when studying the physiological properties of drugs and chemicals to inquire not only into their zoopharmacological effects on living animals and their tissues but also into their phytopharmacological properties or their effects on living plants⁵⁶. Such studies have been found extremely useful for investigating the biological effects on growth of minute quantities of hormones and vitamins⁵⁷, and phytopharmacological experiments have also been helpful in detecting the presence of certain toxins in the blood of various diseases of man^{58, 59}. Experiments were conducted on the growth of *Lupinus albus* seedlings in solutions of heparin in different concentrations, under standard conditions of light, temperature and other ecological factors. It was found that heparin in certain concentrations exerted an auxin-like action on the root growth of *Lupinus albus* seedlings under these conditions. Detailed data on the subject are reserved for publication in a more technical journal of plant physiology. The subjoined data, however, give some idea of the results obtained. Table 3 shows a definite stimulation in growth of seedlings placed in solutions of heparin 1:20,000, in plant-physiological saline and allowed to grow in the dark for 24 hours at 20° C. It will be noted that a synthetic homologue of heparin, the sodium salt of polyanethol sulfuric acid, exhibited no such growth-stimulating effect but, on the contrary, produced inhibition of root growth.

TABLE III

Effect of Concentrations of 1:20,000 of Heparin on Growth of *Lupinus Albus* Seedlings at 20° C for 24 Hours

Brand of Heparin	Index of Growth
H W & D, Lot C (1:100)	108 per cent
H W & D, Lot D (1:80)	110 per cent
H W & D, Lot E (1:100)	109 per cent
H W & D, Lot X (1:50)	117 per cent
Swedish	108 per cent
Canadian	112 per cent
Swiss	108 per cent
Na polyanethol sulfuric acid	66 per cent

These observations on plants are of interest not only insofar as they confirm the low toxicity of heparin for plants as well as of animals but also in connection with the writer's laboratory experiments, the results of which indicate that heparin solutions in vitro neutralize the toxicity of poisonous substances encountered in the blood of certain diseases. Whether these findings made in the test tube will hold good for clinical trials it is impossible to say now but the writer is investigating this subject in an endeavor to discover if repeated injections of heparin modify to some degree the clinical progress of various pathological conditions.

Keeping Qualities of Heparin A description of the general pharmacology and toxicology of heparin would be incomplete without a brief ref-

erence to the stability of heparin preparations. Heparin has been found by all investigators to be a stable compound which maintains its potency for a long time. Although highly purified samples kept at room temperature for several months occasionally lose some of their potency, owing probably to some internal change or rearrangement of the molecules, sterile solutions of heparin in hard-glass ampules have been found by us to retain their potency for long periods of time. The author has carried out extensive experiments on the effect of drastic treatment of heparin, in powder form and in solution, with various physical agents and was surprised to find that such exposure effected very little change in the physiological activity of the drug.

TABLE IV
Effect of Physical Agents on Stability of Heparin

1 Heating in autoclave 20 minutes at 15 lbs pressure	no change
2 Prolonged exposure to sunlight	no change
3 Exposure to polarized light of visible spectrum	no change
4 Irradiation with mercury quartz lamp for one hour	no change
5 Exposure to roentgen-rays, 1000 r	slight weakening
6 Exposure to 1000 gamma ray units of radium emanations	slight deterioration
7 Agitation by high frequency oscillators	no change
8 Extremely high mechanical pressure	no change

The Absorption of Heparin and Duration of Its Effect The rapid absorption and excretion or disappearance of heparin from the blood stream after injection in lower animals and human beings and the consequent brevity of its anticoagulant effect present the chief obstacle to its wider use in therapeutics. All workers in this field have found that heparin injected in quantities more than sufficient to keep shed blood fluid for many hours outside the body did not retard coagulation time in vivo for more than one hour after administration. In practice it is, therefore, necessary to resort either to frequent injections of this drug or to its administration by slow infusion into a vein by the so-called drip method, trying to the patient and exhausting to the pocketbook. The writer has been studying the absorption of heparin through various portals of entry in an endeavor to find some means of prolonging its anticoagulant effect. The following is a brief summary of the findings made.

Even large doses of pure heparin administered to animals by mouth or stomach tube have no effect on coagulation time of their blood. Local applications of heparin solutions to mucous membranes such as those of the mouth in the sublingual region were also ineffectual in this respect. Small doses, 1 to 5 mg of heparin (1:100), subcutaneously or intramuscularly injected in rabbits and cats, did not appreciably retard coagulation time. When much larger doses, e.g., 50 mg, were thus given to small rabbits, coagulation time was occasionally delayed in samples of blood drawn 15 to 20 minutes after injection, but not later. Intraperitoneal injections of heavy doses, 50 to 100 mg of heparin (1:50) were little more effective than injections into the muscle, i.e., slight anticoagulant effect was noted 15 to 30

minutes after its administration, but not later than 45 minutes after. Experiments were also made with suspensions and emulsions of heparin in oil injected into the muscles. These were no more effective than intramuscular injections of aqueous solutions. Implantation in experimental animals of pellets containing heparin covered with a protective substance had no effect as far as prolongation of its anticoagulant action was concerned.

It has, therefore, hitherto been the practice of all investigators to resort to intravenous injections for the study of heparin in both experimental and therapeutic cases. Unfortunately even massive doses of the drug thus injected into the vein in the author's experience have been found to exert their greatest potency only within a limited period of time. The most powerful anticoagulant effect after such injections occurred from 10 to 30 minutes after injection and in the majority of experiments on cats and rabbits the

Duration of Effect of Heparin Administered to Rabbits by Various Routes

Rabbit A, weighing 2 kilo

October 21, 1941—Normal coagulation time—9 min., 20 sec

Injected 5 mg of heparin (1:50) in muscles of leg

After 20 minutes, coagulation time—9 min., 15 sec

After 35 minutes, coagulation time—9 min., 10 sec

After one hour, coagulation time —9 min

Rabbit B, weighing 2.5 kilo

October 21, 1941 Normal coagulation time—8 min., 25 sec

Injected 5 mg of heparin (1:50) into ear vein

After 30 minutes, coagulation time—12 minutes, 5 sec

After one hour, coagulation time — 2 minutes

Cat No 5, weighing 3.0 kilo

April 6, 1942—normal coagulation time—10 minutes

2:58 p.m., injected in vein 10 mg of heparin (1:80)

3:08 p.m., coagulation time 57 minutes

3:24 p.m., coagulation time 37 minutes

3:46 p.m., coagulation time 23 minutes

3:59 p.m., coagulation time 17 minutes

4:11 p.m., coagulation time 11 minutes

4:18 p.m., coagulation time 9 minutes

anticoagulant effect vanished within an hour after administration of the drug and was usually superseded by a compensatory rebound or shortening of the coagulation time as compared with the normal. The protocols exemplify the usual results obtained in cats and rabbits after intramuscular and intravenous injections of the drug.

The Absorption of Heparin through Bone Marrow How to prolong the typical antithromboplastic effects of heparin is still an unsolved problem, but results of experiments recently carried out in this laboratory point to another approach to solution of this riddle. Within the past few years diverse reports have appeared in the medical literature concerning the transfusion of blood and plasma through the bone marrow. The brilliant work

of Morrison and Samwick,⁶⁰ and of Tocantins⁶¹ and O'Neill,⁶² is especially noteworthy in this connection. The former investigators have successfully injected blood and bone marrow cells into the marrow of various patients, and the latter have developed a satisfactory technic of transfusing plasma, glucose solutions and whole blood in animals and human beings by a similar route.

The present writer for many years has been engaged in a study of the absorption of drugs and poisons through various portals of entry into the body.⁶³ In this connection it was found that aqueous solutions were readily absorbed through the bone marrow and thus produced their characteristic pharmacodynamic effects.⁶⁴ Of special interest in this connection, however, were the findings made with different kinds of oils. The so-called essential or volatile oils are rapidly absorbed when injected into the medullary cavity of long bones and produce depression of the nervous system, convulsions, coma and death, depending on the dose injected. The fixed oils, such as olive oil, sesame oil, peanut oil, cottonseed oil, when injected into the bone cavities, acted very differently. No toxic effect was noted after injection of such oil and it was surprising to find that no fat or oil embolism occurred in experimental animals. It was further found that when active pharmacological principles, such as epinephrine, were suspended in a fixed oil like olive oil and introduced into the tibia of a rabbit, cat or dog, the absorption of the epinephrine was very slow, the result being a characteristic rise in blood pressure which was sustained for a long time, 35 to 45 minutes, a result quite

Rabbit D, weighing 2.5 kilo

October 21, 1941 Normal coagulation time—9 min, 20 sec

Injected 5 mg of heparin (1:50) suspended in 0.8 cc of olive oil into cavity of right tibia

After 25 minutes, coagulation time—24 minutes

After 50 minutes, coagulation time—11 minutes

After one hour and 40 minutes, coagulation time—14 minutes

Cat No 6, weighing 2.0 kilo

April 7, 1942 Normal coagulation time—5 min

2:31 p.m., injected 2 mg of heparin, lot No 10 (1:80), dissolved in 0.4 cc of saline in cavity of right tibia

2:32 p.m., injected 4 mg of heparin, lot No 10 (1:80), suspended in 0.6 cc of olive oil into cavity of right tibia

2:45 p.m., coagulation time 21 minutes

3:03 p.m., coagulation time 9 minutes

3:17 p.m., coagulation time 20 minutes

3:33 p.m., coagulation time 22 minutes

3:48 p.m., coagulation time 12 minutes

4:03 p.m., coagulation time 12 minutes

4:18 p.m., coagulation time 12 minutes

4:30 p.m., coagulation time 12 minutes

4:50 p.m., coagulation time 12 minutes

5:00 p.m., coagulation time 12 minutes

5:10 p.m., coagulation time 12 minutes

unlike that obtained by intramedullary injections of the same drug in aqueous solutions. These experiments suggested a similar technic for the study of heparin with the object of prolonging its antithromboplastic effect. Suspensions and emulsions of pure heparin were made in olive oil and small quantities of these were slowly introduced into the tibia and other long bones. It was found that such a procedure effected a slow absorption of heparin and extended its anticoagulant action for a much longer time than did intravenous injection of the drug. Numerous control experiments with injections of olive oil and other fixed oils in small quantities revealed that such injection of oils into the bone cavities were usually not injurious and fat embolism occurred only in rare and exceptional instances. The heavy oil employed in the animal experiments appeared in some way to retard the absorption of heparin and acted as a reservoir releasing the drug in small quantities into the circulation and ensuring its action for a much longer time than it could be maintained after intramedullary administration of aqueous solutions of the anticoagulant. The protocols are a typical illustration of the results obtained.

COMMENT

In addition to its hormone-like regulation of blood coagulation, heparin possesses other pharmacological properties of considerable interest. The decrease in toxicity of ouabain and digitalis for heparinized cats, as compared with normal animals, and similar findings regarding lethal dosage of cobra venom and congo red may or may not be correlated with their antithromboplastic property. The present writer's observations on the effects of digitaloid glucosides, cobra venom and congo red on coagulation, however, certainly lend some support to this view. Moreover these findings suggest that a tendency to intravascular clotting and a predisposition to thrombo-embolic accidents in certain pathological conditions or in the course of administration of certain drugs may be of commoner occurrence than hitherto suspected. Poisons of endogenous or exogenous nature may be responsible for precipitating such catastrophes and when such a contingency threatens, administration of heparin may be considered as a rational prophylactic measure. The complexity of the subject is shown also by the recent observations of Winternitz and his coworkers, who studied the effects on blood pressure and circulation of injections of various tissue extracts with and without heparin and noted divergent results in two series of experiments.

Equally interesting is the antagonistic action of heparin for certain forms of anaphylactic shock. Here again, that phenomenon in some obscure fashion may be correlated with anticoagulative properties of the drug. Such a hypothesis may warrant a clinical trial of heparin as a prophylactic measure to mitigate the severe reactions liable to follow injections of various sera and vaccines. Certainly the low toxicity of heparin, which is reported in this paper, and shown by extensive previous observations of fellow work-

ers, renders such a prophylactic procedure harmless and supports the view that heparin is a hormone-like normal product of the animal metabolism continually secreted or elaborated for maintenance of normal physiological functions of the blood

The low toxicity of heparin for animals and plants appears to warrant its more liberal employment in a clinic. More puzzling, however, are the great stability and resistance of heparin to physical agents, on the one hand, in contrast to its rapid absorption and equally rapid disappearance in the body, on the other. How to prolong the duration of its anticoagulant action more satisfactorily than by intravenous injection is a problem still unsolved, although the results of experiments on animals with intramedullary administration of oily suspensions and emulsions of the drug are very suggestive in this connection. It is astounding to learn, as in the present writer's experience, that oil or fat embolism, hitherto the nightmare of the experimental pathologist, is but a rare occurrence so far as serious or even mild injury to lower animals is concerned after intramedullary injection of fixed or heavy oils. Nevertheless, it would be hazardous to conclude that the data yielded by tests on rabbits and cats may be transferred per se to the practice of human therapeutics.

SUMMARY

1 Specimens of purified heparin of high potency are remarkably resistant to acute treatment with physical agents, heat, ultraviolet rays, roentgen-rays, radium emanations and various mechanical manipulations.

2 Heparinization of cats prior to intravenous injections of ouabain and digitalis solutions significantly lowers the toxicity of these drugs. This difference in toxicity is probably correlated with a thromboplastic effect of digitaloid glucosides observed in vitro.

3 The toxicity for cats of cobra venom and congo red, intravenously injected, is also diminished by prior heparinization of the animals.

4 Large doses of heparin injected into guinea pigs sensitized with horse serum tend to prevent anaphylactic shock or to reduce its violence.

5 Massive doses of pure heparin have no toxic effect on the circulation and respiration, the kidney and liver function, the central nervous system or the neuromuscular behavior of animals.

6 Aqueous solutions of heparin in concentrations of 1:20,000 to 1:80,000 exert a stimulating or auxin-like effect on root growth of *Lupinus albus* seedlings reared under standardized plant-physiological conditions.

7 The anticoagulant effect of heparin on intramuscular or intraperitoneal injection is inconstant and negligible. Intravenous injections of the drug usually exert an antithromboplastic effect for not more than one hour after administration. Intramedullary injection of cats and rabbits with heparin suspended in fixed oils or emulsions prolongs its anticoagulant action.

8 All of these findings, obtained in laboratory experiments on animals and plants, must not be regarded per se as applicable without reservation to human therapeutics. However, they serve as a starting-point or stimulus for further physiological and pharmacological research on the subject and give some hint of eventual usefulness in medical practice.

BIBLIOGRAPHY

- 1 McLEAN, JAY The thromboplastic action of cephalin, *Am Jr Physiol*, 1916, xli, 250-257
- 2 HOWELL, W H The coagulation of blood, *Harvey Lectures*, 1916-1917 volume, Series XII, 272-323
- 3 HOWELL, W H, and HOLT, E Two new factors in blood coagulation, heparin and thrombosis, *Am Jr Physiol*, 1918, xlvii, 328-341
- 4 HOWELL, W H, and McDONALD, C H Note on effect of repeated intravascular injections of heparin, *Bull Johns Hopkins Hosp*, 1930, xli, 365-368
- 5 JORPES, J E Heparin, its chemistry, physiology and application in medicine, 1939, Oxford University Press, London
- 6 MASON, M F Heparin review of its history, chemistry, physiology and clinical applications, *Surgery*, 1939, v, 451 and 618
- 7 CRAFOORD, C Preliminary report on post-operative treatment with heparin as preventive of thrombosis, *Acta chir Scandinav*, 1937, lxxix, 407-426
- 8 CRAFOORD, C Heparin and post-operative thrombosis, *Acta chir Scandinav*, 1939, lxxxii, 319-333
- 9 MURRAY, D W G, JAQUES, L B, PERRETT, T S, and BEST, C H Heparin and vascular occlusion, *Canad Med Assoc Jr*, 1936, xxxv, 621-622
- 10 MURRAY, D W G, JAQUES, L B, PERRETT, T S, and BEST, C H Heparin and thrombosis of veins following injury, *Surgery*, 1937, ii, 163-187
- 11 SOLANDT, D Y, and BEST, C H Heparin and coronary thrombosis in experimental animals, *Lancet*, 1938, ii, 130-132
- 12 CRAFOORD, C Heparin as prophylactic against postoperative thrombosis, *Acta med Scandinav*, 1941, cvii, 116-122
- 13 CRAFOORD, C, and JORPES, J E Heparin as prophylactic against thrombosis, *Jr Am Med Assoc*, 1941, cxvi, 2831-2835
- 14 BEST, C H Heparin and thrombosis, *Harvey Lecture*, *Bull New York Acad. Med*, 1941, xvii, 796-817
- 15 LEISSNER, H Use of heparin in obstetric practice as means of preventing thrombosis, *Acta med Scandinav*, 1941, cvii, 127-130
- 16 CLASON, S Three cases of pulmonary embolism following confinement treated with heparin, *Acta med Scandinav*, 1941, cvii, 131-135
- 17 PLOMAN, K G Heparin treatment of thrombosis in central vein of retina, *Acta ophth*, 1938, xvi, 502-512
- 18 HOLMIN, N, and PLOMAN, K G Thrombosis of central vein of retina treated with heparin, *Lancet*, 1938, i, 664-665
- 19 BOSTROM, C G, and WILLIAM-OLSSON, L Thrombosis of central vein of retina successfully treated with heparin, second case, *Lancet*, 1938, ii, 78-79
- 20 FERGUSON, R R Thrombosis of inferior temporal branch of right retinal vein successfully treated with heparin, *Jr Am Med Assoc*, 1941, cxvii, 1351-1352
- 21 KELSON, S R New method of treatment of subacute bacterial endocarditis using salicypyridine and heparin in combination, preliminary report *Jr Am Med Assoc*, 1940, cxiii, 1700-1702
- 22 LEACH, C E and others Chemotherapy and heparin in subacute bacterial endocarditis, further experiences, *Jr Am Med Assoc*, 1941, cxvii, 1345-1350

- 23 CHARLES, A F, and SCOTT, D A Studies on heparin, preparation of heparin, Jr Biol Chem, 1933, cii, 425-429
- 24 BERGSTROM, S, JORPES, E, and WILANDER, O Studies on pure heparin, Scandinav Arch f Physiol, 1937, lxxvi, 175-185
- 25 CHARGAFF, E Studies on chemistry of blood coagulation, protamines and blood clotting, Jr Biol Chem, 1938, cxxv, 671-676
- 26 HOLMGREN, H, and WILANDER, O Beitrag zur Kenntnis der Chemie und Funktion der Ehrlichschen Mastzellen, Ztschr f mikr anat Forsch, 1937, xlii, 242-278
- 27 MACHT, D I Influence of barometric changes on potency of digitalis for cats, Am Jr Physiol, 1931, xcvi, 540
- 28 ABEL, J J, and MACHT, D I Two crystalline pharmacological agents obtained from the tropical toad, Bufo agui, Jr Pharmacol and Exper Therap, 1912, iii, 319-377
- 29 RUDOLPH, C Various uses of congo red in diagnosis, prognosis and therapy, Med Jr and Rec, 1933, cxxxvii, 296-297
- 30 BELONOSCHKIN, B, and WOHLISCH, E Über die angebliche Neubildung von Fibrinogen durch Kongorot, Klin Wchnschr, 1933, xii, 1371-1372
- 31 BECKER, J Blutstillung durch Kongorot, vorläufige Mitteilung, Munchen med Wchnschr, 1930, lxxvii, 396-397
- 32 GREEN, W L Congo red in treatment of certain infections, preliminary report, J Indiana Med Assoc, 1937, xxx, 527-529
- 33 MACHT, D I, HARDEN, W C, and GRUMBEIN, M L Toxicological studies on congo red, Jr Am Pharm Assoc, 1939, xxviii, 495-498
- 34 TALIAFERRO, I, and HAAG, H B Toxicity and effect of congo red on blood coagulation, Am Jr Med Sci, 1937, cxciii, 626-633
- 35 RICHARDSON, A P Congo red hematologic reactions, Am Jr Med Sci, 1939, cxcviii, 87-97
- 36 MACHT, D I Experimental and clinical study of cobra venom as an analgesic, Proc Nat Acad Sci, 1936, xxi, 61-71
- 37 MACHT, D I Therapeutic experiences with cobra venom, ANN INT MED, 1938, xi, 1824-1833
- 38 MACHT, D I Recent developments in the pharmacology and therapeutics of cobra venom, Med Rec, 1941, cliii, 369-375 and 379
- 39 MICHEEL, F, and BODE, G Zur Kenntnis der Schlangengifte, Ber d deutsch chem Gesellsch, 1938, lxxi, 1302
- 40 KYES, P, and STRAUSSER, E R Heparin inhibition of anaphylactic shock, Jr Immunol, 1926, xii, 419-422
- 41 WILLIAMS, O B, and VAN DE CARR, F R Effect of heparin on anaphylactic shock in guinea pigs, Proc Soc Exper Biol and Med, 1927, xxiv, 798-800
- 42 MACHT, D I, DUNNING, F, and STICKEL, A E Influence of heparin injections on anaphylactic shock, Am Jr Physiol, 1928, lxxxi, 390
- 43 HANZLIK, P J, BUTT, E M, and STOCKTON, A B Reciprocal action of crop muscles in anaphylactic shock with note on effects of heparin, Jr Immunol, 1927, xiii, 409-425
- 44 REED, C I, and LAMSON, R W Influence of heparin on course of anaphylaxis in guinea pig, Jr Immunol, 1927, xiii, 433-438
- 45 WILANDER, O Complete blood analysis of heparinized blood, Acta med Scandinav, 1938, xciv, 258-266
- 46 JACQUES, L B, and WATERS, E T Identity and origin of anticoagulant of anaphylactic shock in dog, Jr Physiol, 1941, xcix, 454-466
- 47 ROCHA F SILVA, M, and DRAGSTEDT, C A Liberation of heparin by trypsin, Proc Soc Exper Biol and Med, 1941, xlviii, 152-155
- 48 DRAGSTEDT, C A, WHITE, J A, and ROCHA F SILVA, M Heparin as an antidote to trypsin in the rat, Fed Proc, 1942, i, 149
- 49 KIRCHHEIM, L Untersuchungen über Trypsinvergiftung, Arch f exper. Path u Pharmacol, 1913, lxxiv, 374-398

- 50 ERSHLER, I L, and BLAISDELL, I H Massive hematuria following use of heparin in cavernous thrombosis, Jr Am Med Assoc, 1941, cxvii, 927-930
- 51 COPLEY, A L, and LALICH, J J The experimental production of a hemophilia-like condition in heparinized mice, Am Jr Physiol, 1942, cccxv, 547-556
- 52 Bleeding from mucous membranes caused by heparin, etc., Jr Am Med Assoc, Queries and Minor Notes, 1942, cxviii, 1526
- 53 The Chemical Dicoumarin, Science, 1942, Supplement \cv, 12-13
- 54 MACHT, D I, and MORA, C F Effect of opium alkaloids on the behavior of rats in the circular maze, Jr Pharmacol and Exper Therap, 1920, \vi, 219-235
- 55 MACHT, D I, and BRYAN, H F Influence des venins de serpent sur le comportement du rat dans un labyrinthe circulaire, Compt-rend Soc. de biol, 1935, c\ix, 306-309
- 56 MACHT, D I Contributions to phytopharmacology or the applications of plant physiology to medical problems, Science, 1930, l\vi, 302-306
- 57 MACHT, D I, and GRUMBEN, M L Influence of indole acetic, indole butyric and naphthalene acetic acids on roots of Lupinus albus seedlings, Am Jr Bot., 1937, \xlii, 457-460
- 58 MACHT, D I The phytotoxic reactions of normal and pathological blood sera, Protoplasma, 1937, \xxvii, 1-8
- 59 MACHT, D I, and MACHT, M B Phytotoxic reactions of some blood sera, Jr Lab and Clin Med, 1941, xxvi, 597-615
- 60 MORRISON, M, and SAMWICK, A A Intramedullary (sternal) transfusion of human bone marrow, preliminary report, Jr Am Med Assoc., 1940, c\i, 1708-1711
- 61 TOCANTINS, L M Rapid absorption of substances injected into bone marrow, Proc Soc Exper Biol and Med, 1940, \iv, 292-296
- 62 TOCANTINS, L M, and O'NEILL, J F Infusion of blood and other fluids into circulation via bone marrow, Proc. Soc Exper Biol and Med, 1940, \iv, 782-783
- 63 MACHT, D I The absorption of drugs and poisons through the skin and mucous membranes, Jr Am Med Assoc., 1938, c\, 409-413
- 64 MACHT, D I Absorption of drugs through the bone marrow, Proc. Soc Exper Biol and Med, 1941, \lvii, 292-302
- 65 MYLON, E, HOFF, H, KATZENSTEIN, R, and WINTERNITZ, M C The fall in blood pressure associated with intravenous injection of tissue extracts, Science, 1941, \civ, 190-191

SUGAR ALCOHOLS XXIV. THE METABOLISM OF SORBITOL IN DIABETES *

By FRED W. ELLIS, PH D, and JOHN C KRANTZ, JR, PH D,
Baltimore, Maryland

SORBITOL was introduced into therapeutics in Europe under the name of "Sionin" by Thannhauser and Meyer¹ in 1929. Since that time various workers have investigated its value as a substitute for carbohydrate in the diabetic diet with no consistent findings. Reinwein² administered sorbitol to diabetics and observed an increase in the respiratory quotient but no rise in blood sugar. On the other hand, Roche and Raybaud³ observed no increase in the respiratory quotient, and Donhoffer and Donhoffer⁴ reported a rise in blood sugar after giving sorbitol to diabetic patients.

Kaufmann⁵ reported that sorbitol exhibited a protein-sparing action and was useful to the diabetic. Gottschalk⁶ ascribed an "insulin-enticing" action to this compound and recommended its use in diabetics. von Noorden⁷ also recommended the use of sorbitol in the diet of mild and moderately severe diabetics. Excellent utilization of sorbitol was observed by Bertrand, Radais and Labbé⁸ in diabetic patients with and without insulin.

In 1933 Payne, Lawrence and McCance⁹ reported that sorbitol was not directly metabolized and was an inert compound which could be used safely as a sweetening agent by diabetics. Raybaud and Roche¹⁰ reported that sorbitol was not a satisfactory substitute carbohydrate and questioned its value in diabetes. In this country Silver and Reiner¹¹ reported that sorbitol produced hyperglycemia in a diabetic patient.

Recently in this country sorbitol has been made available at a comparatively low cost and its possible continued use as an item of diet in normal individuals has received much attention.

Ellis and Krantz¹² observed that 25 or 50 gm of sorbitol increased the respiratory quotient of normal individuals as much as an equal amount of dextrose. At the same time, sorbitol did not significantly elevate the blood sugar.

The present investigation is concerned with the effects of sorbitol on the respiratory quotient and the blood-sugar level in mild and moderately severe diabetics.

Experimental Thirteen patients were made available for this study by the staff of the University Hospital. Details of the conditions under which this work was done were similar to those previously described¹². In each experiment 50 gm of dextrose or sorbitol were given orally to the patient.

* Received for publication June 10, 1942.

From the Department of Pharmacology, School of Medicine, University of Maryland. The expense of this work was defrayed in part by a grant from the Atlas Powder Company of Wilmington, Delaware.

TABLE I

Patient	Time	50 Gm Dextrose		50 Gm Sorbitol	
		Blood Sugar mg per cent	Respiratory Quotient	Blood Sugar mg per cent	Respiratory Quotient
N B	Fast	153	0.75	152	0.70
	$\frac{1}{2}$ hr	180	0.75	167	0.75
	1 hr	221	0.78	165	0.75
	2 hrs	232	0.79	156	0.73
A D	Fast	140	0.80	154	0.75
	$\frac{1}{2}$ hr	194	0.77	167	0.76
	1 hr	222	0.79	180	0.80
	2 hrs	235	0.87	151	0.80
H R	Fast	157	0.76	181	0.70
	$\frac{1}{2}$ hr	190	0.72	173	0.70
	1 hr	190	0.71	166	0.73
	2 hrs	211	0.77	166	0.74
J L	Fast	153	0.68	169	0.70
	$\frac{1}{2}$ hr	178	0.67	173	0.70
	1 hr	200	0.73	175	0.72
	2 hrs	189	0.80	166	0.72
K T	Fast	256	0.70	227	0.70
	$\frac{1}{2}$ hr	308	0.69	227	0.70
	1 hr	312	0.74	223	0.65
	2 hrs	308	0.77	225	0.71
I E	Fast	136	0.70	133	0.72
	$\frac{1}{2}$ hr	164	0.70	140	0.74
	1 hr	189	0.70	143	0.76
	2 hrs	200	0.74	143	0.75
L M	Fast	140	0.73	138	0.70
	$\frac{1}{2}$ hr	224	0.71	136	0.72
	1 hr	222	0.70	133	0.72
	2 hrs	222	0.75	135	0.70
M P	Fast	163	0.63	146	0.64
	$\frac{1}{2}$ hr	224	0.64	151	0.71
	1 hr	244	0.62	148	0.72
	2 hrs	225	0.66	141	0.71
R M	Fast	122	0.71	125	0.73
	$\frac{1}{2}$ hr	140	0.73	121	0.77
	1 hr	170	0.76	120	0.75
	2 hrs	190	0.79	120	0.76
C B	Fast	143	0.71	133	0.66
	$\frac{1}{2}$ hr	174	0.76	143	0.68
	1 hr	200	0.74	133	0.76
	2 hrs	222	0.76	133	0.75
D S	Fast	133	0.73	143	0.83
	$\frac{1}{2}$ hr	161	0.70	121	0.80
	1 hr	134	0.77	123	0.80
	2 hrs	120	0.87	110	0.75
A E	Fast	136	0.68	156	0.61
	$\frac{1}{2}$ hr	200	0.70	158	0.66
	1 hr	235	0.74	154	0.68
	2 hrs	250	0.77	151	0.67
I. S	Fast	116	0.61	111	0.65
	$\frac{1}{2}$ hr	157	0.71	126	0.64
	1 hr	172	0.78	133	0.65
	2 hrs	162	0.78	135	0.70

and the influence of the two compounds on the blood sugar and respiratory quotient was compared

The results of individual experiments are shown in table 1 and the average values are shown graphically in chart 1

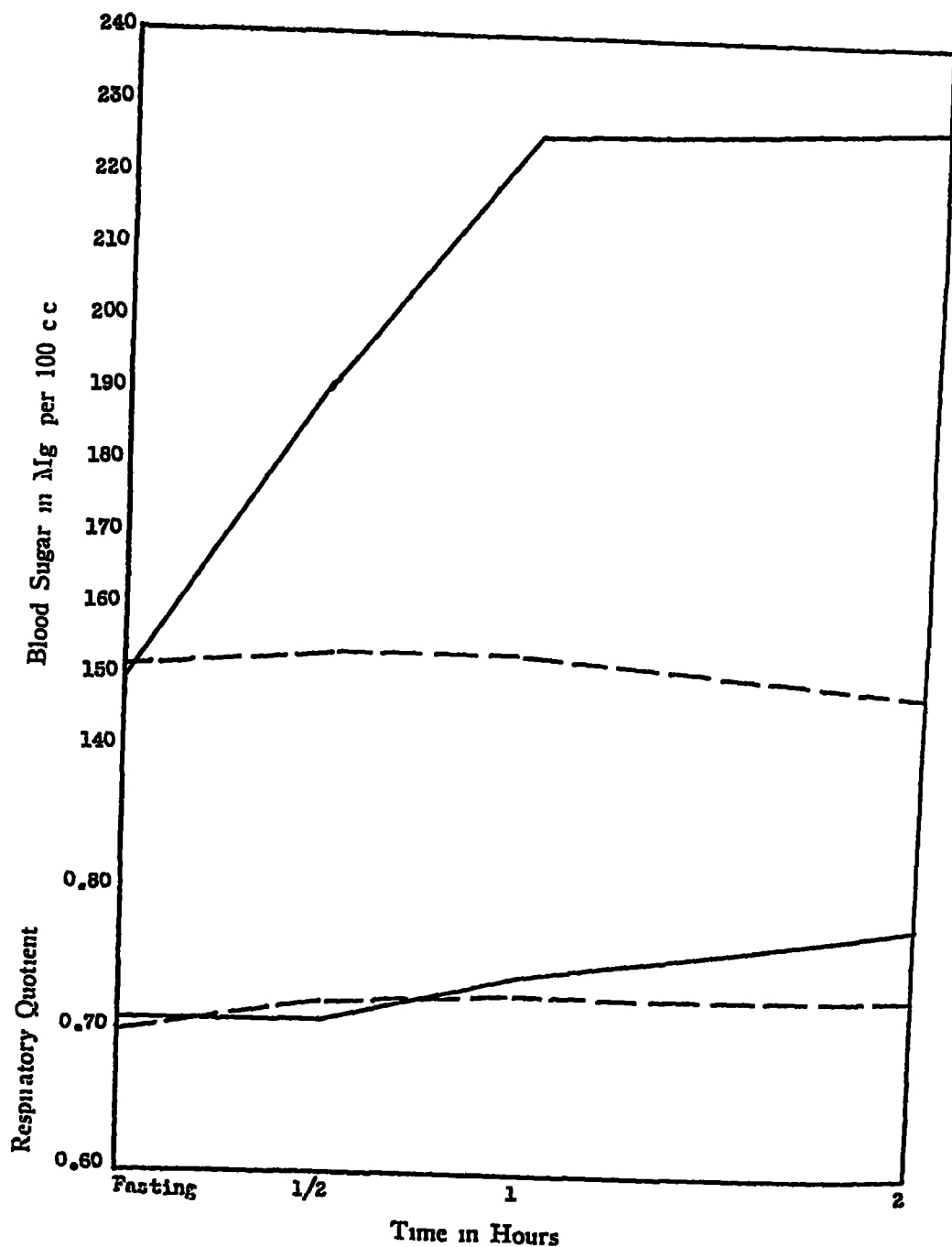


CHART 1 Influence of dextrose and sorbitol on the blood sugar and respiratory quotient of diabetics Average of 13 cases Solid line, dextrose, broken line, sorbitol

DISCUSSION

It was shown previously that sorbitol significantly elevates the respiratory quotient of normal individuals when ingested in 25 and 50 gm quantities

This occurs without a concomitant hyperglycemia. If these phenomena occurred in the diabetic it would strongly indicate utilization without drain on the impaired insulin stores. However, in the rat and *Rhesus macacus* monkey sorbitol serves as a precursor of hepatic glycogen and in all probability the same metabolic pattern obtains in man. It is obvious from an examination of chart 1 that sorbitol does not significantly raise the respiratory quotient of the diabetic. This strongly suggests the improbability of its direct utilization in the diabetic. In the liver sorbitol is converted to levulose¹⁸ and polymerized into glycogen. It would follow, therefore, that when glycogenolysis occurs providing for glucose utilization in the periphery, insulin would be required for its catabolism. Thus after depolymerization of glycogen, of which sorbitol is a precursor, the fate of glucose and sorbitol in the body is likely identical, each requiring insulin. This in turn bespeaks that its use in diabetes must be in accordance with the patient's residual tolerance for glucose or his insulin dosage. Whether glucose and sorbitol, gram for gram, require the same or different amounts of insulin for their utilization has not yet been determined. This problem is still under investigation in this laboratory in depancreatized dogs.

There remains, however, another consideration in the use of sorbitol in the diabetic diet. When ingested, sorbitol produces no significant postprandial hyperglycemia. As it is absorbed from the alimentary tract there is, however, a likelihood of a high blood-sorbitol level. As sorbitol is a non-reducing carbohydrate-like substance (sugar alcohol) its presence in the blood is not made manifest by the usual methods of determining blood-sugar. The absorbed sorbitol is oxidized to levulose, polymerized to glycogen and depolymerized to glucose. These conversions are orderly time reactions and prevent a plethora of glucose from appearing in the blood, which occurs immediately after the ingestion of the latter. Undoubtedly the absence of a precipitous hyperglycemia from the regimen of the diabetic exerts a benign influence on his carbohydrate tolerance, for large quantities of carbohydrates fed to partially depancreatized dogs cause characteristic lesions (hydropic degeneration) in the β cells of the islet tissue and in the diabetic reduce further the carbohydrate tolerance. The relative effects on the impaired islet tissue of a hyperglycemia and a high blood-sorbitol level, to our knowledge, have not yet been investigated. We consider this an important phase of this question of the ultimate advantage or danger of sorbitol in the diabetic, and as yet it remains unanswered.

SUMMARY

In 13 mild and moderately severe diabetic patients sorbitol failed to influence significantly either the blood-sugar level or the respiratory quotient. Its place in the diabetic diet has been discussed.

BIBLIOGRAPHY

- 1 THANNHAUSER, S J, and MEYER, K H Sorbit (Sionin) als Kohlehydratersatz für den Diabeteskranken, München med Wchnschr, 1929, lxxvi, 356
- 2 REINWEIN, H Über die Verwertbarkeit des d-Sorbit in der Behandlung des Diabetes mellitus, Deutsch Arch f klin Med, 1929, clxiv, 61
- 3 ROCHE, A, and RAYBAUD, A Sur l'utilisation de la sorbite par l'organisme, Compt-rend Soc de biol, 1933, cxiii, 320
- 4 DONHOFFER, S, and DONHOFFER, M Über die klinische Untersuchung des Kohlenhydratstoffwechsels mittels d-Sorbit, Deutsch Arch f klin Med, 1930, clxvii, 257
- 5 KAUFMANN, E Ein neuer Kohlenhydratersatz zur Diabetesbehandlung, Klin Wchnschr, 1929, viii, 66
- 6 GOTTSCHALK, A Die Bedeutung der Ersatzkohlenhydrate für die Praxis und Theorie der Zuckerkrankheit, Ergebn d inn Med u Kinderh, 1929, xxxvi, 56
- 7 VON NOORDEN, K H Sionin in der Diabetesbehandlung, Deutsch med Wchnschr, 1929, iv, 483
- 8 BERTRAND, G, RADAIS and LABBÉ, M Sur l'emploi de la sorbite dans l'alimentation des diabetiques, Bull Acad de méd, 1934, cxii, 8
- 9 PAYNE, W W, LAWRENCE, R D, and McCANCE, R A Sorbitol (Sionin) for diabetics, Lancet, 1933, ccxxv, 1257
- 10 RAYBAUD, A, and ROCHE, A Valeur dietetique de la sorbite dans la cure diabete sucre, Presse méd, 1934, xlii, 172
- 11 SILVER, S, and REINER, M Essential fructosuria, Arch Int Med, 1934, liv, 412
- 12 ELLIS, F W, and KRANTZ, J C, JR Metabolism and toxicity studies with mannitol and sorbitol in man and animals, Jr Biol Chem, 1941, cxli, 147
- 13 EMBDEN, G, and GRIESBACH, W Über das Schicksal des d-Sorbit und einiger anderer Hexite, Ztschr f physiol Chem, 1914, xci, 251

MÉNIÈRE'S SYNDROME AND MIGRAINE; OBSERVATIONS ON A COMMON CAUSAL RELATIONSHIP*

By MILES ATKINSON, M D , F R C S (ENG), *New York City*

THE possibility of a relationship between migraine and the syndrome known as Ménière's was suggested by Ménière himself in his original paper. Although later observers have also seen the possibility, only recently has any satisfactory basis been established for the mechanism of either, so that hitherto the theory of a relationship has had to depend upon clinical observation and conjecture rather than upon the result of experiment. It has been probability rather than fact. The object of this paper is to attempt to show that the two conditions have an actual causal relationship, the basis of both being a vascular dysfunction.

Definition When conditions so polymorphic as paroxysmal headache and paroxysmal vertigo are to be studied, it is essential that a clear-cut definition of the class of case under consideration be given. When the two are to be compared this desideratum is even more important. It has been in part the failure to do this which has led in the past to the diversity of opinion and therapeutic claim in the case of both conditions. O'Sullivan¹⁰ has brought out this point very effectively in her migraine studies.

The definition of migraine given by Brain³ is of "a paroxysmal disorder characterised in its fully developed form by visual hallucinations and other disturbances of cerebral function, associated with unilateral headache and vomiting." Migraine, however, is a condition which shades off from the fully developed form into a great number of lesser variants, so that by some observers almost any periodic headache will be accepted as migraine. In this paper a somewhat less rigid definition than that quoted will be adopted, though one with very definite limits. It is proposed to accept as migraine cases of severe paroxysmal unilateral headache associated with gastrointestinal disturbances, arising at puberty or soon after and persisting until middle life or later, but it will not be insisted that there should *necessarily* be disturbances of cerebral function to establish the diagnosis. Only cases conforming strictly to this pattern will be called migraine.

Similarly with Ménière's syndrome, variations in severity of symptoms and in the chronology of their appearance are common. Vertigo may be mild and may at times precede deafness and tinnitus by months and even years. For the purpose of this paper, however, only those cases have been acceptable which have shown the complete classical syndrome of severe attacks of paroxysmal vertigo associated with increasing deafness and tinnitus.

Such self-denying ordinances, although they limit the material available,

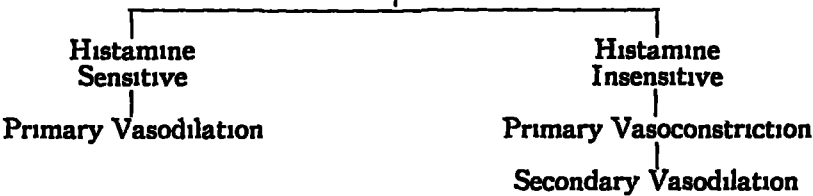
* Received for publication August 1, 1942.

Read before the Section of Neurology and Psychiatry at the Annual Meeting of the American Medical Association, Atlantic City, June, 1942.

are essential to the establishment of the thesis Only when this has been achieved will it be permissible to relax definition

The Mechanism of Ménière's Syndrome (Table 1) It has been shown, it is believed satisfactorily, that cases of Ménière's syndrome can be divided into two groups by means of an intradermal test with histamine (Atkinson ²)

TABLE I
The Dual Mechanism in Ménière's Syndrome

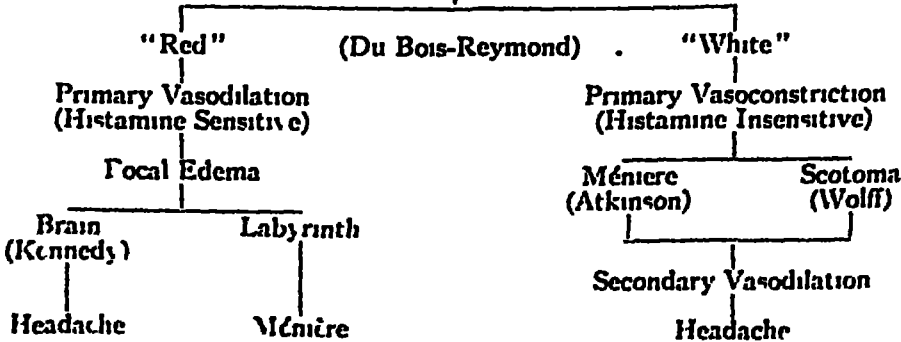


(1) First there is a small group which is sensitive to histamine, which has a primary vasodilator or, more orthodoxly, an allergic basis, and which can be satisfactorily treated by desensitization to histamine or by elimination of the specific antigen when such can be discovered

(2) There is a second group, the large majority, which is insensitive to histamine, and in which the attacks are the result of a primary vasospasm Cases in this group can be relieved, in the great majority of cases, by the exhibition of vasodilator drugs, of which the most satisfactory in the writer's hands has proved to be nicotinic acid This advocacy of a particular drug, however, is not intended to imply that vasospasm is due to one single factor, any more than that the manifestations of allergy are produced by one single antigen The precipitating factors of vasospasm are probably many, but concern at the moment is not with them What is of concern here is the principle, the vasospasm

The Mechanism of Migraine (Table 2) In this condition also there is evidence of a dual etiology, of the same nature as that which applies in Ménière's syndrome

TABLE II
The Dual Mechanism in Migraine



(1) The thesis of allergy as a cause of migraine attacks was put forward and upheld by Kennedy,⁶ and has been very generally accepted as applying correctly at least to a portion of the cases

(2) On the other hand, Wolff and his collaborators¹¹ have shown that migraine attacks can be the result of a primary vasospastic process, that the preliminary visual disturbances are vasospastic in origin and can be abolished by the inhalation of amyl nitrite in small doses, and that the headache itself is the result of a secondary compensatory vasodilation. This accords in all respects with the writer's findings in the second, or histamine insensitive, group of Ménière cases

These two groups correspond with the "red" and "white" migraine of du Bois Reymond, a classification which has been commonly decried in recent years but which appears increasingly to have validity

Association of the Migraine Syndrome with Ménière's Syndrome
What it is sought to establish, however, is not only an identical mechanistic basis but an actual etiological relationship, a relationship like that which joins, for instance, all pneumococcal manifestations together into one family by virtue of their dependence upon a specific organism, as against the broader tie of bacterial diseases in general. For this there is clinical evidence

Headache not uncommonly accompanies or is associated with Ménière attacks. Mygind and Dederding⁷ found the association in 19 per cent of their cases, but did not define the type of headache they referred to. I have found headache in general to be a much more usual accompaniment of Ménière's syndrome. In some form or another it has been present in 63 out of 108 cases, just over 58 per cent. Twenty-two of these could be classed as clear-cut migraine, or 20 per cent of all cases, a figure practically the same as that of Mygind and Dederding. Moreover, the laterality of the headache, or its predominant laterality in cases not invariably on the same side, has in every instance been the same as that of the deaf or deafer ear. Finally, migraine, migraine strictly according to the letter of the law, has been found to occur in both groups of Ménière cases (tables 3 and 4)

TABLE III
Numbers in Present Series

<i>Total Ménière Cases</i>	108
Vasodilator Group	20
Vasoconstrictor Group	88
<i>Cases with Migraine</i>	22
Vasodilator Group	10
Vasoconstrictor Group	12
<i>Cases with Non-Specific Headache</i>	42
Vasodilator Group	6
Vasoconstrictor Group	36
<i>Cases with out Headache</i>	44

The Vasodilator (Allergic) Group Twenty cases of Ménière's syndrome have fallen into this group, and 10 of these (50 per cent) have also

TABLE IV
Ménière Cases Associated with Migraine
Results of Treatment on Headache

	No Treatment	No Change	Improved	Relieved
Vasodilator Group, 10	5	0	1	4
Vasoconstrictor Group, 12	5	0	4	3

suffered from migraine Of the 10, four were not treated for their allergy, three not returning to Clinic and being untraceable, the other having an operation for eighth nerve section which relieved her dizziness though other symptoms, among them headache, continued to be severe and disabling, and in a fifth case the migraine attacks had ceased some years before she was seen on account of vertigo The remaining five have been treated by desensitization to histamine as described elsewhere² In four instances the migraine attacks have been abolished coincidentally with the Ménière attacks, in the fifth case the migraine has been considerably improved both as regards frequency and severity, and the Ménière manifestations have ceased

The Vasoconstrictor Group Of 88 Ménière cases in this group, 12 have had classical migraine (13.6 per cent) In five cases the migraine had ceased before or coincidentally with the onset of Ménière attacks The seven remaining cases in which migraine attacks still occurred have been treated for their Ménière's syndrome without regard to their migraine, in the manner described elsewhere² for cases of the vasoconstrictor group, with nicotinic acid In all seven, vertigo has been relieved over periods varying from 18 months in the oldest case to six months in the most recent, and in all cases for periods considerably longer than previous intermissions At the same time their migraine has been improved, in the case of four very considerably, three of them so much that they have maintained that they are well of it though admitting that they still have an occasional mild headache, and the other have been relieved entirely of headache for periods (as of December, 1941) of 8, 12, and 15 months

The Chronology of Migraine Headache in Relation to Ménière Attacks There is an interesting and characteristic difference in the timing of the headache in relation to the vertigo in the two groups

1 Vasodilator (Allergic) Group In the smaller group of histamine sensitive patients, the headache *precedes* the vertigo and serves in some sort as an aura It may start as many as 24 hours before and is, at any rate at first, unilateral on the side of the deaf ear Gradually it increases in intensity until it becomes an intense, bursting pain of great severity which, when it reaches its height, explodes like a rocket in a dizzy attack For a few moments vertigo is extreme, then it gradually subsides and disappears leaving behind only an aftermath of unsteadiness At the height of the attack the patient usually vomits, then feels completely exhausted and finally

falls into deep sleep from which he awakes more or less recovered. Such an episode might be called with equal justification a migraine attack with vertigo or a Ménière attack with headache.

2 Vasoconstrictor Group In the much larger group of histamine insensitive patients, the headache *succeeds* the vertigo instead of preceding it as in the previous group. With little or no warning, the patient is seized with vertigo of considerable severity, even severe enough to knock him down, and in the cases under discussion this is immediately followed by a headache having the characteristics of migraine. The sequence is vertigo followed by unilateral headache on the deaf side, nausea and perhaps vomiting, rapid relief of extreme vertigo, gradual relief of headache. Evidently here the vertigo of a Ménière attack is the equivalent of the visual disturbances of migraine.

In both groups, but especially in the vasoconstrictor group, either symptom may occur on occasions without the other—headache without vertigo, vertigo without headache. Presumably on these occasions the vasospasm is more restricted in its area of impact.

Scotoma and Vertigo It appears, then, that the scotoma of migraine and the vertigo of Ménière are the result of the same mechanism, a vasospasm of cerebral vessels acting in different situations. Moreover, the disparity between these two situations is not in fact so wide as it seems at first if the origin of the vascular supply rather than its termination is considered. The auditory artery which supplies the labyrinth is a branch of the basilar artery, the posterior cerebral which supplies the occipital lobe is its terminal branch. Thus a migraine headache may follow a labyrinthine disturbance just as well as a visual disturbance, and vertigo can take the place of scotoma as the pre-headache phase of an attack which in the one instance is called Ménière and in the other migraine.

Furthermore, just as vertigo often occurs without succeeding headache in Ménière's syndrome, so scotomata may occur without succeeding headache in the later years of a migraine history (Case 3). Occasionally even a scotoma may arise without headache having ever been a symptom, though other manifestations of a migraine diathesis are present (Case 4). Such cases are apt to be a puzzle unless they are recognized for what they are, a part of the migraine syndrome. They have the same mechanism as the scotomata of migraine, the vertigo of Ménière—vasoconstriction, and they can be relieved by measures directed to overcoming it.

Conversion of Migraine Syndrome into Ménière's Syndrome In yet other instances, one manifestation leads to the other—the "sick headache" of youth turns into the Ménière attack of middle age (Case 2). This was the case in five instances in this series, all belonging to the vasoconstrictor group. Sometimes there is an interval between the two of several years, sometimes the Ménière attacks follow immediately upon the cessation of the migraine. "My headaches stopped when my dizzy attacks started" (251542, Clinic). Moreover, these patients commonly do not have the complete syn-

drome Their migraine in the past may not have been preceded by visual disturbances, and later their Ménière attacks are not necessarily directly associated with headache, though unassociated headache without all the migraine characteristics is frequent

A reasonable explanation seems to be that in the years of youth the vasospasm is minimal, producing inconspicuous symptoms or none at all, though these patients can sometimes recall, especially if specifically questioned, occasional blurring of vision or occasional mild dizziness in attacks in earlier years, minor matters which were disregarded in the severity of the headaches The succeeding relaxation, however, the youthful rebound, as it were, is maximal and produces the characteristic headache As time goes on, and age, combined no doubt with the effect of repeated insult, diminishes the resilience of the vessels, the secondary vasodilation which used to produce the headache ceases to occur All that happens now is the spasm, but that the more effectively because of the lessened vascular elasticity

Migraine and Hypertension It is an old clinical observation that migraine patients tend to "grow out of" their headaches, which presumably means that at least their secondary dilation gradually ceases to occur It is now coming to be recognized that they may also "grow into" something else There are the five cases already mentioned here in which migraine has given way to Ménière attacks A parallel observation of the merging and changing of migraine into another condition with age has been made by Gardiner and his associates,⁶ who have shown that migraine sufferers in youth tend to become hypertensives with age The observation fits in with the hypothesis put forward here It must be admitted, however, that patients with Ménière's syndrome are not necessarily, nor indeed usually, afflicted with hypertension Indeed, contrary to the popular view, among the older patients in the presumably degenerative group a high blood pressure is the exception rather than the rule Perhaps hypertension involves among other things a stiff, unyielding vascular tree which prevents the degree of both contraction and relaxation necessary for a paroxysmal attack, so that a patient with the migraine diathesis may develop hypertension or Ménière attacks, but not both This, if it is so, is a beneficent dispensation of Providence, for to have both would be too much

"Formes Frustes" In order to forestall criticism, a very rigid criterion of diagnosis has been adopted for the purpose of this paper But in practice many cases of headache with Ménière attacks occur which, though they do not comply absolutely with this definition of migraine, nevertheless might be and usually are accepted by the clinician as minor variants or "formes frustes" For instance, many Ménière cases complain of periodic headache not clear-cut enough to be labeled classical migraine (table 3) yet often mainly unilateral and on the side of the deaf ear, and it is remarkable how frequently the headache in these cases clears up with the institution of treatment directed towards the Ménière attacks Many patients say very early in treatment that, whereas their vertigo has been diminished

though not yet abolished, the main improvement they notice is in their headaches which have disappeared. On the other hand, there are also many cases of undeniable migraine who complain of some degree of dizziness yet who are not acceptable as Ménière cases because they do not have the complete syndrome. Some of these patients actually show in an audiogram an early cochlear involvement on the affected side of which they are quite unaware (figure 1)

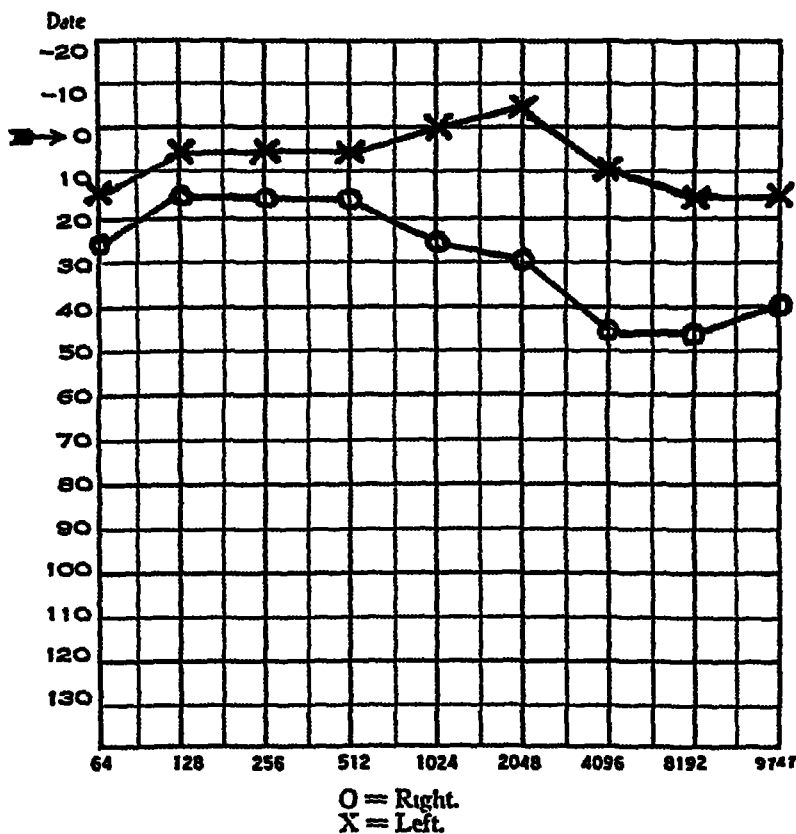


FIG 1 Audiogram from case of a woman of 37 who had suffered from right-sided migraine since childhood and who was unaware of impaired hearing on that side

It is in these intermediate cases that confusion of diagnosis occurs. When headache predominates such patients tend to be seen by the neurologist and to be called migraine, when vertigo predominates they tend to be seen by the otologist and to be called Ménière's disease, when both symptoms are present, the two fight over the body. Actually if the thesis put forward here is accepted, whether headache or vertigo predominates matters not at all. The fundamental process is the same, only the locale differs. Etiologically speaking, Ménière's syndrome is aural migraine.

Therapeutic Response As important a piece of evidence as any is that of therapeutic response. All these patients have been treated as for Ménière's syndrome by methods which have already been described elsewhere.² No special therapeutic attention has been paid to their headaches,

yet the results as regard headache have been as satisfactory and as lasting as have the results as regard vertigo (table 4). In the vasodilator or allergy group, desensitization has relieved headache and vertigo together. In the vasoconstrictor group weekly headaches which previously had been relieved by ergotamine temporarily have been relieved for many months following the use of nicotinic acid combined with conventional general measures. And this is not surprising when the primary vasoconstrictor mechanism of migraine is borne in mind. Ergotamine in therapeutic doses is a vasoconstrictor drug, and relieves headache by overcoming the secondary vasodilation which produces it. It does nothing to prevent its recurrence. Nicotinic acid, as a vasodilator, attacks the basic process, vasoconstriction. It goes to the root of the matter, by preventing the primary phase it also prevents the secondary. Moreover a number of cases which do not conform to the strict definition demanded here, cases of migraine without vertigo or of atypical headache with vertigo, have given satisfactory results with treatment on the same lines. They lend a certain collateral support to the thesis.

It must again be insisted here, as I have already insisted elsewhere² in considering Ménière's syndrome alone, that the advocacy of nicotinic acid for treatment is not meant to imply that these conditions are vitamin deficiency diseases. Nicotinic acid is used solely as a vasodilator, on the assumption that it acts on central vessels as it does on peripheral, as a vasodilator. For this there is increasing evidence^{3, 4} despite some evidence to the contrary^{7, 4}.

DISCUSSION

The evidence brought forward indicates, it is hoped satisfactorily, that the syndrome of Ménière and the syndrome of migraine are identical in as far as concerns the mechanism of their production, which is a vascular one. Where they differ is in the location of the impact—in the one case it is upon the labyrinth, in the other upon the cerebral hemisphere. What determines location or laterality is not as yet apparent.

The two syndromes differ, too, in the frequency of occurrence of the two groups. Whereas in Ménière's syndrome the primary vasodilator group is a relatively small one compared with the vasoconstrictor, in the migraine syndrome the position, if not reversed, is at least more nearly equal. Allergy as a cause of migraine is common, as a cause of paroxysmal vertigo it is uncommon. This fits in with the age groups in which the two syndromes arise—paroxysmal headache is a condition of youth, like the vasodilation which produces it, paroxysmal vertigo a condition of middle life or later, like the vasoconstriction which is its usual cause.

Finally, to repeat a point already insisted upon, nicotinic acid is used in the treatment of the vasoconstrictor group not because it is part of the vitamin B complex, but because it is a powerful capillary vasodilator. Nicotinic acid is used as the type substance to overcome vasoconstriction when the cause cannot be found, just as histamine is used as the type substance to test

for and desensitize against a general allergy when the specific antigen is not known. Neither method absolves us from a search for the specific cause if such can be found. But since in the present state of knowledge these specific causes are frequently unknown or undiscoverable, an understanding of the basic mechanism will when necessary permit of the effective use of a non-specific remedy. It is this basic vascular mechanism which presumably explains the satisfactory results reported with such divergent substances as thiamin chloride and estrogens—both have a certain vasodilator action apart from their specific replacement function.

SUMMARY

1 The two groups into which cases of Ménière's syndrome can be divided have been shown to correspond etiologically to two groups of migraine cases.

2 Many instances arise in both groups of cases in which the two conditions are coincidental and apparently related, or in which migraine attacks merge into Ménière attacks.

3 The mechanism of both groups is discussed and an hypothesis put forward to explain the clinical phenomena observed.

4 Treatment which has proved successful in relieving the vertigo of patients with Ménière's syndrome has also relieved the migraine headache in those cases in which it also has been present.

5 Treatment of this syndrome, whether characterized in the main by vertigo or by headache, to be successful depends upon accurate grouping of cases. No single method will achieve success in all cases, for there is more than one cause.

CASE REPORTS

Case 1. A Case of Severe Ménière Attacks (Vasodilator Type) Associated with Migraine Headaches. A woman aged 28 (1937) complained of attacks of vertigo of varying severity weekly for four months with slightly impaired hearing and tinnitus in the right ear. Since adolescence she had suffered from migraine, occasionally with blurring of vision. These migraine attacks had at one time occurred weekly, then had become less frequent, but since her dizzy spells they had become more frequent again and ushered in the attacks of vertigo. Examination of the ears showed slight impairment of hearing of conductive type on the right side and vestibular hypofunction on the right. Other examinations and investigations were negative. At that time she was put on sedation and a dietary regime and was not seen again for two years.

In February 1939 she returned with a story of improvement—headaches less frequent and less severe, a few mild dizzy spells—until two weeks previously when she had a severe attack of headache and vertigo followed by another the day before being seen. Hearing had somewhat deteriorated but was variable, as also was tinnitus. On examination the findings were the same as before except for a marked increase in hearing loss and this time a histamine skin test was done which was markedly positive. Desensitization to histamine was undertaken and for 12 months she had no dizziness or headache though she still had occasional tinnitus and the hearing loss remained stationary. Then her headaches started to return and a few days later

though a dizzy spell impended. She was given a short course of histamine injections, after the first of which symptoms disappeared and she has since been free of vertigo and almost of headache for 12 months (August, 1941).

Case 2 A Case in Which Ménière Attacks (Vasoconstrictor Type) Followed upon Cessation of Migraine A woman aged 53 had suffered from severe predominantly right-sided migraine from age 10 to 25. This improved after marriage and her migraine eventually disappeared, though she had occasional headaches of indefinite nature. Then at age 33 she suddenly had a succession of mild dizzy spells ushered in by one severe one which occurred after a week of tinnitus and impairment of hearing in the right ear. Attacks continued to occur in batches, varying in severity, at intervals of two to three months, until she was seen (1940) following a series of rather unusually severe attacks. During the previous two years, headaches had returned, now without migraine characteristics, and had been getting more severe. The dizzy spells were typical Ménière attacks, and as usual findings were negative except as regards diminished function in the affected (right) ear. She fell into the histamine insensitive group and was consequently treated with nicotinic acid, since which time she has suffered no more dizzy spells (eight months). During this time she has had three mild headaches, not migraine in type—"the sort of headache I imagine everyone has once in a while, nothing like I used to have."

Case 3 A Case of Migraine Followed by Ménière Attacks in Which Eventually Headache Ceased but Scotoma Remained A man aged 45 had suffered from left-sided migraine of considerable severity for 25 years, usually with visual disturbances. Seven years ago (1934) he had experienced his first dizzy spell, and attacks of vertigo had continued to occur during the next 13 months, accompanied by deafness and tinnitus. Then tinnitus and vertigo ceased, and deafness improved as far as he could tell to normal. Two years later (1937) he experienced four weeks of tinnitus without vertigo or apparently impairment of hearing. In 1939 he had three months of vertigo, deafness and tinnitus, and this time the deafness and tinnitus persisted though the vertigo ceased. In 1941 (March) he again had attacks lasting until seen. During these seven years his migraine headaches had gradually diminished in frequency and severity, and for the previous three months, the period of his most recent bout of Ménière attacks, they had virtually ceased (very occasional and very slight left frontal pain only), but scotoma and fortification spectra had occurred without headache. Examination demonstrated the usual absence of positive findings apart from the ear (diminished left cochlear function). The histamine skin test was negative, putting him in the vasoconstrictor group, and treatment on the appropriate lines was recommended. Unfortunately it has not been possible to follow up this patient.

The great interest of the case is in the onset or persistence of vasoconstrictor mechanisms—vertigo and scotoma, with the gradual failing and ultimate disappearance of the secondary vasodilator phenomenon of headache.

Case 4 A Case Showing a Scotoma without Headache but with Other Migraine Manifestations A woman aged 39 years in 1938, two and a half years before being seen, had noticed a left paracentral scotoma which appeared suddenly at the end of a busy day spent largely under arc lights. This confused the issue at first, making a Kleig burn seem probable, but subsequent events invalidated this diagnosis. The scotoma slowly increased in size and intensity for three months, then as gradually faded away. At no time was there complete loss of vision, but sight was blurred and objects appeared as through a fog. Spots and flashes of light were common, but she never experienced fortification spectra, and the degree of impairment was very variable. Sometimes the fog would be thin and the scotoma small, at others thick and the scotoma large. These changes could happen very suddenly. The whole episode lasted about six months. A second similar episode occurred a year later, again after considerable stress, and she was in the third when first seen.

There were certain other significant points in the history. She had never suffered from headaches, but there was a family history of migraine, asthma, hay fever and eczema. She herself had suffered from "bilious attacks" since the age of 15 and had to be careful of her diet. For some years she had been subject to bouts of sneezing, especially on rising in the morning. Two months before the scotoma appeared for the first time, also after a long and busy day, she had a sudden attack of weakness, collapse and "black-out" with a pulse that dropped to 50 for 15 minutes, or more. This sudden bradycardia had returned on many subsequent occasions, though only for two or three minutes at a time and always during periods when the scotoma was present, though it was not synchronous with the onset of the scotoma. Alcohol, in the form of a cocktail, undoubtedly was capable of diminishing the size of the scotoma and the density of the fog, an observation made on several occasions. An injection of ergotamine on one occasion produced no improvement, if anything it made matters worse.

Examination revealed nothing of significance, apart from the ophthalmological findings, and a somewhat excessive weight. Nor was there anything of significance in the eye examination apart from the variable left paracentral scotoma. Laboratory investigations contributed no information of help. Basal metabolic rate was -2 , sedimentation rate 7, sugar tolerance normal. A histamine skin test was negative.

It was assumed that the mechanism at work was a vascular one comparable to that producing migraine and Meniere attacks, that the scotoma represented a condition comparable to the pre-headache phase of migraine, and that it was vasoconstrictor in type in view of the normal histamine reaction. This assumption received added support when an injection of acetylcholin 0.1 gm produced an improvement in the size and depth of the scotoma. She was consequently treated on vasodilator lines with nicotinic acid, at the same time being given a mildly reducing diet of high protein high vitamin content and a small dose (gr $\frac{1}{2}$) of thyroid extract daily. She was also urged to reorganize her life, to live at a slower pace and under less extreme conditions. This of course she did not do. Nevertheless she started to improve immediately after treatment was instituted (it may be that it chanced to be instituted at a lucky moment) and continued to improve rapidly, more rapidly according to her own testimony than she had ever done before. In two months the scotoma had almost disappeared, vision had improved, she had lost 15 lbs in weight and was feeling in much better general health. In six months there has been no set back, even though she has been grossly overworked and has had two attacks of a vasovagal nature in that time. A very small scotoma remains which has not varied in four months and which one fears may represent permanent damage. It does not bother her. What is equally worthy of note is that since she has followed this regime, she finds that she can tolerate foods which formerly she could not (tomatoes, chocolate, fats) and her sneezing has ceased. Though it is too early to be certain of success in view of relapses in the past, the improvement in collateral symptoms under treatment suggests that it is properly directed and that the assumed mechanism may be correct.

BIBLIOGRAPHY

1. ARING, C. D., RIDER, H. W., ROSEMAN, E., ROSENBAUM, M., and FERRIS, E. B. Effect of nicotinic acid and related substances on the intracranial blood flow of man. *Arch Neurol and Psychiat*, 1941, **46**, 649.
2. ATKINSON, M. Observations on the etiology and treatment of Meniere's syndrome. *Jr Am Med Assoc*, 1941, **116**, 1753.
3. BRAIN, W. R. *Diseases of the nervous system*. 1935 Oxford University Press. 1000 pp.
4. FORBES, H. S. Personal communication.
5. GARDINER, J. W., MOUNTAIN, G. E., and HINES, E. A. The relationship of migraine to hypertension and to hypertension headaches. *Am Jr Med Sci*, 1940, **cc**, 59.

- 6 KENNEDY, F Migraine—a symptom of focal brain edema, New York State Jr Med, 1933, xxxiii, 1254
- 7 LOMAN, J, RINKEL, M, and MYERSON, A The intracranial and peripheral vascular effects of nicotinic acid, Am Jr Med Sci, 1941, ccii, 211
- 8 MOORE, M T Treatment of multiple sclerosis with nicotinic acid and vitamin B₁, Arch Int Med, 1940, lkv, 1
- 9 MYGIND, S H, and DEDERDING, D Clinical and experimental examinations in patients suffering from Mb Meniere, Act Otolaryngol, Supps 10 & 11, 1929
- 10 O'SULLIVAN, M E The present day status of migraine therapy, Endocrinology, 1939 xxiv, 414
- 11 WOLFF, H G, CAHAN, A M, and SCHUMACHER, G A Studies of migraine the contrast of vascular mechanism in headache, and pre-headache phenomena, Proc. Am Neurol Assoc, 66th Annual Meeting, June 6-9, 1940

ARACHNOIDITIS (DIFFUSE PROLIFERATIVE LEPTOMENINGITIS) *

By ALEX BLUMSTEIN, M D , and A B BAKER, M D ,
Minneapolis, Minnesota

CHRONIC or subacute low-grade leptomeningitis, cystic and adhesive in nature, is a clinicopathologic condition known by a number of names in medical literature (arachnoiditis, serous meningitis, meningitis serosa circumscripta vel cystica, arachnoiditis adhesiva circumscripta and diffusa) For the sake of simplicity and because of widely accepted usage in this country, the term arachnoiditis is used in this title although it is obviously inaccurate

The cystic structures are not cysts in the true sense of the word They are in reality collections of cerebrospinal fluid walled off by meningeal adhesions The fluid within the cysts is often under great tension The leptomeningitis may be predominantly cystic or predominantly adhesive The extent of the arachnoiditis varies from a well-localized lesion to a diffuse process involving the entire cerebrospinal axis There is, however, a definite tendency for the process to be either cerebral or spinal Arachnoiditis may be primary or it may be secondary to pathologic changes in adjacent structures †

In some instances the etiology can be ascertained This is especially true in the localized (circumscribed) form in which trauma has been shown to play an important part The clinical picture, the course, and the response to treatment are extremely variable, depending upon the location, the extent and the cause of the process

The cerebral type of arachnoiditis is usually focal in type but rarely it may be diffuse Demel¹ collected reports of 40 cases of the localized type The clinical picture was that of brain tumor In 16 cases the lesion was in the posterior fossa Recovery followed in approximately 90 per cent of cases operated upon Horrax² reported 33 cases simulating cerebellar tumor, 28 were followed from one to nine years, and all showed improvement or complete relief from symptoms Lillie³ reported three cases of prechiasmal syndrome produced by arachnoiditis He indicated the possibility of preoperative diagnosis and the favorable results from proper surgical treatment

For purposes of discussion, spinal arachnoiditis may be divided into the localized and the disseminated types Generally, writers on the subject of

* Received for publication February 14, 1942

From the Division of Nervous and Mental Diseases, University of Minnesota Medical School, Minneapolis, Minnesota

† In the various types of encephalitis and in other diseases of the central nervous system leptomeningeal thickening is a not infrequent pathologic finding. In these instances, however, the leptomeningeal thickenings do not necessarily produce symptoms. Here we are concerned only with the type of arachnoiditis which causes symptoms.

spinal arachnoiditis group all the cases together regardless of the extent of the process. This gives an exceedingly varied and complex clinical picture. The tendency to put all cases into a single group is due in part to the clinical difficulty of differentiating the two types. However, as Stookey ⁴ points out, the subject would be less confusing if a real effort were made to place the disseminated and localized types in separate categories for the purpose of analysis. In the following discussion an effort will be made to distinguish between the circumscribed and the disseminated types. If that is not possible, the term arachnoiditis will not be qualified.

Elkington ⁵ reported 41 cases of arachnoiditis collected at National Hospital, Queens Square. There were 30 males and 11 females. The youngest case was 23 years of age, the oldest 65. The average age of the patients when first seen was 45 years. The age grouping was as follows:

Under 20—	0 cases
20–30—	6 cases
30–40—	6 cases
40–50—	14 cases
50–60—	10 cases
60–70—	5 cases

One of the cases reported by us is that of a 17-month-old boy. Elkington refers to the case of an 8-year-old boy reported by Heller. In Elsberg's ⁶ 38 cases, men and women were equally affected.

As to causes, Elkington's 41 cases are divided in the following manner:

- 9 cases—Injury. The interval between injury and symptoms varied from three weeks to 24 years. The severity of the injury was inconstant.
- 4 cases—Syphilis.
- 2 cases—Meningococcic meningitis.
- 4 cases—Gonorrhea.
- 16 cases—"Systemic" infection.
- 18 cases—No known cause.

Ten of 12 cases of spinal arachnoiditis reported by Stookey had had typhoid fever, influenza, encephalitis, or meningitis. Trauma as a forerunner of arachnoiditis (localized?) is reported particularly by Mauss and Kruger ⁷. In 54 laminectomies in cases of individuals who suffered war wounds, they found arachnoiditis 23 times. In 14 of the 23 cases there was direct trauma of vertebrae. In nine cases there was no direct vertebral trauma. The authors attributed these cases to concussion associated with momentary dislocations of the vertebral bodies. They reported good results from operative intervention. As to causes of the disseminated type, Selinsky ⁸ reported that five of eight cases had had pneumonic or pleuritic infections. Mackay ⁹ reported five cases of the disseminated type, three seemed to result from some form of acute meningitis—one five weeks, one

17 years, and one five years previous to the arachnoiditis. In two cases there was no known cause. Barker and Ford¹⁰ reported a case of the disseminated type in which arachnoiditis set in during convalescence from lymphocytic choriomeningitis. Laboratory studies revealed the virus.

Clinical Picture There is a gradual onset without fever. Invariably the disease assumes a subacute or chronic course. In Stookey's 12 cases of arachnoiditis, six had symptoms for more than seven years. In Elsberg's series there was a history of symptoms for from one to more than nine years. The disseminated type produces a syndrome of multiple involvement of the spinal nerve rootlets, both anterior and posterior, but predominantly posterior. *Pain is the most distinctive symptom.* It usually commences over one or more spinal segments and later becomes bilateral and spreads over a wide cutaneous area. The pain often has a burning, constricting quality and is frequently influenced by posture, movement of the spine, straining and coughing. The pain may occur over widely separated areas and may be accompanied by hyperesthesia or diminished sensation. The objective sensory disturbances are often vague, bizarre, or inconstant in distribution. Diminished reflexes and muscular atrophy which can best be explained on the basis of anterior rootlet involvement are not infrequent. If the cauda equina is involved there is atrophy and hypotonia of the legs. Bladder and rectal disturbances come late in the disease, as a rule there is urgency long before incontinence sets in.

There may be slight or, in later cases, considerable involvement of the spinal cord. A cyst may produce signs and symptoms of compression like a true neoplasm. If the cyst is part of a disseminated process, there will be signs simulating extramedullary tumor in addition to the features of multiple rootlet involvement. This will lead to slowly progressive weakness and spasticity of the extremities, impaired sensibility, exaggeration of tendon reflexes, pathologic plantar responses, and impairment of sphincters. Constriction of the spinal cord by adhesions may cause a similar picture.

In 50 per cent of Elsberg's cases, cells and total protein were well within normal limits. Stookey made manometric studies in 10 cases, five had almost complete block and five showed partial block. Even in some cases of subarachnoid block, the protein content of the fluid was normal and xanthochromia was absent. Increase in cells is rare in arachnoiditis. In Elkington's series, cytologic studies were made in 26 cases with normal results in 25. In one case there were 50 and 42 lymphocytes per cu mm on two separate occasions.

In Selinsky's eight cases of disseminated arachnoiditis all showed scattered arrest of iodized oil after cisternal injection. The arrest of lipiodol at multiple levels is pointed out by a number of writers. Schwartz and Deery¹¹ describe small linear shadows due to droplets of oil spread over portions of the meninges. Scattered droplets of oil in the subarachnoid space generally retain a globular shape. However when the oil lodges

against thickened dentate ligaments and subarachnoid fibers, small linear horizontally placed shadows are produced on the film

Robertson¹² reported five cases of arachnoiditis. He made the pre-operative diagnosis in three of the cases, using the following points

- 1 Extensive area affected by the pain which was of burning quality and characterized by periods of remission
- 2 The intimate relation of pain to posture (such as raising the arm)
- 3 Evidence of dissemination of the process
- 4 Evidence of involvement of motor roots (atrophy and diminished reflexes)

The pain is intense and is frequently associated with hyperesthesia. In two of our cases the pain was intractable and disabling. The duration of the symptoms is usually much longer in arachnoiditis than in cord tumor. The initial pain frequently extends over a larger area than in cord tumor (for example, an entire extremity). The distribution of the pain is difficult to reconcile with a single compressing lesion. Anesthesia is generally not so pronounced as in spinal tumor, unless there is marked constriction. A history of previous subarachnoid infection is helpful in the diagnosis of arachnoiditis. The arrest of iodized oil at multiple levels is a most important diagnostic aid. Subarachnoid block without xanthochromia or increased protein is a highly suggestive corroborative finding in arachnoiditis. The onset of arachnoiditis is much slower than in encephalo-myelo-radicularitis¹³. In the latter there is rarely subarachnoid block and the course is very much more benign. In encephalo-myelo-radicularitis there is, as a rule, absence of muscle atrophy and fairly complete recovery despite the severity and extensiveness of the nervous system involvement. In arachnoiditis there is rarely cell protein dissociation. Evidence of upper and lower motor neuron involvement in arachnoiditis may lead to a mistaken diagnosis of amyotrophic lateral sclerosis. This occurred in one of our cases and in a case reported by Robertson. However, pain is rarely a prominent feature of amyotrophic lateral sclerosis and subarachnoid block practically never occurs.

Treatment Elsberg states "Whatever may be the cause for the leptomeningeal adhesions, it can not be denied that the adhesions may disturb the functions of the spinal cord and nerve roots by direct pressure, and by interference with the vascular supply of the cord aggravate a preëxisting intramedullary lesion. Therefore, in the present state of knowledge, exploratory laminectomy is generally indicated". "The adhesions are most often found on the posterior and lateral aspects of the spinal cord and especial attention must be paid to the emerging nerve roots, and any bands constricting them must be divided."

In referring to roentgen-ray therapy for disseminated arachnoiditis, Schinsky states "In my experience, no other nonsurgical therapeutic measure has exerted such a favorable influence. The spine is crossfired with high voltage radiation at the various levels indicated by the sensory disturbance.

One or more series of treatments are given, depending on the response to therapy. If indicated, the series of treatments is repeated at intervals of six weeks. Fractional treatments are given at each sitting and consist of from 100 to 150 roentgens (in air) until a total of 800 roentgens is administered. According to Selinsky "High voltage roentgen therapy exerts a definitely ameliorating effect which is variable in duration. Recurrences of the pain may be relieved by a repetition of the treatment." He reported "good results" in four of eight cases. Operation was done in Mackay's five cases of the disseminated type, two died, two were unimproved, and one was clinically benefited.

From a pathologic study of our cases of disseminated arachnoiditis, the outlook for therapeutic improvement from either roentgen-ray or surgical intervention after the process has been long established, does not appear at all promising. In our four cases the cord damage appeared to be due to vascular involvement with associated tissue destruction rather than compression of the nervous tissue by the thickened meninges.

Elsberg states "The outlook after operation will depend to a considerable extent upon the intramedullary changes that have occurred. If the adhesive process is well localized and the symptoms have not been of more than one or two years' duration, the patient may be relieved of all or almost all disturbances by the operation." "If the adhesive process extends over a great part of the spinal leptomeninges, the outlook for improvement is small. However, some of these patients may be improved if by good fortune or good judgment, a part of the cord which has been most compromised by the adhesive process has been exposed and adhesions which compressed the cord have been divided or the contents of a cyst evacuated." Elsberg analyzed 38 cases from his personal experience. "In more than one-half the patients, little or no improvement followed the surgical intervention." "In about 25 per cent of the patients in whom the adhesive process appeared localized with or without compression of the cord by bands, and in whom the symptoms were of less than two years' duration there was considerable improvement in the spastic paraplegia and the sensory disturbances, so that bedridden individuals were able to be up and about again, bladder disturbances, when they existed, were not relieved, and the patient remained an invalid."

In about 25 per cent of Elsberg's patients the relief was complete or almost complete, so that the individuals were able to return to their work and usefulness. In the majority of these patients the relief was permanent.

Pathologic Findings In chronic diffuse leptomeningitis there is grossly a definite thickening of the leptomeninges throughout the entire length of the spinal cord. Usually this involvement is not uniform being more marked at certain levels and in certain regions at a single level. In the more involved areas the membranes are opaque and completely obliterate the underlying structures.

In Elkington's series, 18 of 41 cases showed at operation a loculated collection of fluid amounting to actual cysts. The most conspicuous abnormal-

mality was in the arachnoid which was often milky and opaque in appearance and contained areas of irregular patchy thickenings. The pia-arachnoid was bound to the dura, the cord, and the nerve roots by adhesions. In some of the cases there was a complete obliteration of the subarachnoid space.

Since there are very few complete autopsy studies reported in this condition, we shall limit the histopathological descriptions to the study of our own cases. Before describing the pathologic changes in chronic diffuse leptomeningitis, it might be advisable to review briefly the structure of the



FIG 1 Thickening of the leptomeninges. These membranes are four times normal thickness and are composed of relatively acellular collagenous tissue. Hematoxylin-eosin stain.

normal spinal pia-arachnoid. The spinal pia is composed of a relatively thin layer of intertwining collagenous fibers which are closely adherent to the surface of the cord. The thickness of this layer varies normally from five to 15 microns. The pia is very vascular and contains a large number of blood vessels. Along those vessels one can normally observe scattered groups of mononuclear cells which often increase in number in inflammatory conditions. The arachnoid is a thin net-like membrane about three times as thick as the pia, measuring about 30 to 40 microns. It is a relatively avascular membrane composed of collagenous fibers and lined on both its inner

and outer surfaces by a thin cellular endothelial layer composed of a single irregular layer of peculiar squamous cells which can usually be identified only by means of special silver stains. There is a definite space between the pia and arachnoid called the subarachnoid space. The latter is traversed by numerous fibrous strands that extend from the arachnoid and are attached to the pia (arachnoid trabeculae). When the leptomeninges are studied in fixed tissue, many of these details cannot be made out. Often the subarachnoid space is greatly narrowed and the leptomeninges are so intimately



FIG 2 Compression of the radial vessels by the thickened pia-arachnoid. There is no complete occlusion of the vessels although their lumina are markedly narrowed. Phosphotungstic acid-hematoxylin stain.

related that they appear as a single structure. They then appear as interlacing bundles of collagenous fibers, the inner portion being vascular and probably representing the pia whereas the outer portion is relatively avascular, somewhat thicker, and represents the arachnoid. The total thickness of the leptomeninges normally would vary from 35 to 55 microns.

Histologically, in arachnoiditis there is a diffuse but irregular thickening of the leptomeninges, their combined thickness often varying from 85 to 215 microns, i.e., two to five times normal (figure 1). Either of the two membranes may be more severely involved, but often they are so intimately

related that it becomes impossible positively to identify the separate membranes. In most areas there is a complete obliteration of the subarachnoid space, although occasionally in the less severely involved areas this space can still be identified although greatly reduced in size. In some cases the thickening of the leptomeninges may become so extensive that the process extends outward to obliterate even the subdural space, the thickened membranes merging with the inner dural layer which, however, can usually be identified by its more dense structure. This thickening of the leptomeninges may or

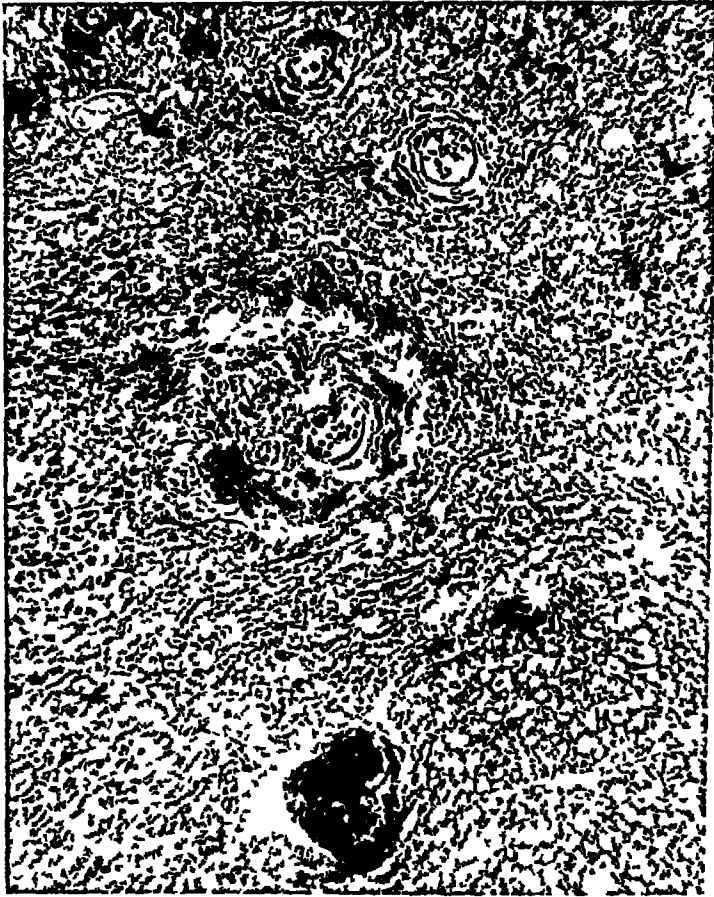


FIG 3 Involvement of one of the smaller paracentral arteries by the thickened leptomeninges
Phosphotungstic acid-hematoxylin stain

may not extend inward to involve the membranes within the anterior and posterior commissures of the cord.

The involved pia-arachnoid shows definite structural variations. It is usually definitely acellular and comprised of dense collagenous tissue. Often it becomes partially or even completely hyalinized, losing all structural characteristics and assuming a homogenous appearance. A few connective tissue nuclei can be found in such cases but even these are pyknotic. Scattered collections of mononuclear cells are occasionally present (figure 1).

The spinal vessels show a most variable degree of involvement. The radial vessels surrounding the cord are invariably compressed by the thick-

ened membranes and many are completely occluded (figure 2). The degree of vascular involvement frequently is in direct proportion to the thickness of the pia-arachnoid. The vascular pia, in some cases, appears entirely devoid of vessels whereas in other cases it shows a definite reduction in its vascularity. The sulcal arteries are usually completely surrounded and often compressed by the thickened membranes resulting, in many cases, in a definite vascular narrowing. In a few areas these vessels are completely occluded and produce a focal softening or even a complete central cavitation within



FIG 4 Narrowing and compression of one of the rootlets as it penetrates the thickened leptomeninges. Note the demyelination of the rootlet and its partial replacement by connective tissue. Phosphotungstic acid-hematoxylin stain.

the spinal cord. Usually the smaller paracentral arteries escape damage, but in an occasional area even those vessels become compressed and occluded (figure 3).

The spinal rootlets as they penetrate these thickened membranes may remain uninvolved, but more commonly they are narrowed, compressed and show definite pathologic alterations. Demyelination is invariably present with a variable degree of destruction of nerve fibers and a secondary fibrous tissue replacement of the involved structures. In some rootlets almost half the fibers appear to have been replaced by a secondary fibrosis (figure 4).

The spinal cord usually shows changes at some levels. These alterations appear to be directly related to the degree of vascular involvement. The meningeal thickening does not appear sufficient to produce cord compression. The cord shows a moderate swelling of the myelin sheaths, often with some patchy vacuolization. In some cases, vascular occlusion produces definite focal areas of softening which involve large areas of a single cord level. Even complete central cavitation may occur, producing a typical syringomyelic picture. The nerve cells are usually uninvolved, although moderate changes may occur in the more severe cases, consisting of swelling, chromatolysis, fragmentation and even complete disappearance. In some cases petechiae occur throughout the gray matter of the cord.

CASE REPORTS

Case 1 On September 1, 1937, H. S., a 57 year old white male, while fixing a tire, stumbled backwards and struck the lower part of his back against a cement curb. He got up without assistance and continued his work. During the following days the base of his spine felt sore, usually becoming worse at night. However, he continued to work regularly. On September 14, two weeks after his injury, he noticed muscular twitching in the right thigh. The next day he had pain and numbness in the lower back and about the right hip. On the same day, while trying to rise from a stooped position, he lost control of both legs. This was followed almost immediately by severe pain extending down to both feet. In three or four hours his legs became completely paralyzed and remained so for about five weeks. He had bowel and bladder incontinence for the first three weeks of that period. He had a patchy sensory loss from the umbilicus down. After three weeks, his urinary difficulty disappeared. However, he did not regain rectal sensation. After five weeks, control of the legs began to return. At the same time he noted gradually increasing stiffness of the legs. A "burning feeling" was associated with the stiffness and return of motion. He was able to walk with some support. He continued to have pain in the lower back and legs.

About 15 years prior to the difficulty already described he had suffered a slight head injury. Six weeks later he had dizziness and pains in the neck. The dizziness was brought on by rotation of the head, and he had some difficulty maintaining his balance. He had no paralysis, and the symptoms disappeared in three weeks.

He was admitted to the University Hospitals on December 23, 1937, at which time the neurologic examination revealed hearing loss on the right, hyperactive deep reflexes in the legs with bilaterally positive Babinski signs, positive Chaddock and Oppenheim signs on the right, left patellar and bilateral ankle clonus, weakness and spasticity of the legs, incoordination of the legs with loss of position sense and diminished vibratory sensibility, absence of pain, temperature and light touch sensibility from the twelfth thoracic segment down. The rest of the physical examination was essentially negative.

The spinal fluid examination revealed a pressure of 10 mm of mercury with no rise on jugular compression, protein, 56 mg per cent, no cells, and serologic tests negative for syphilis. Urinalysis and routine blood studies were normal.

Röntgen-ray report "Lipiodol examination of the spine was done radiographically and fluoroscopically after the injection of 225 cc of lipiodol into the cisterna magna. At the beginning of the examination all of the lipiodol was in the upper cervical spine and cisterna. After putting the patient in the upright position the lipiodol moved very slowly through the cervical canal and met a temporary obstruc-

tion at approximately the level of the first thoracic vertebra. After approximately four to five hours in the upright position there was still lipiodol retained at the level of the sixth thoracic, eleventh thoracic and second lumbar vertebrae. A few droplets had dropped down into the sacral canal. In one of the lateral views at the level between the first and second lumbar vertebrae there was a suggestion of posterior bulging into the canal from the intervertebral disc. Findings suggest an arachnoiditis.



FIG 5 Arrest of lipiodol at multiple levels in a case of arachnoiditis

together with the possibility of multiple ruptures of the intervertebral discs. A definite diagnosis can not be made" (figure 5).

On January 11, 1938, the lamina of the first and second lumbar and the twelfth thoracic vertebrae were removed, and there was apparently some encroachment on the cord at this level. There was no pulsation of the cord. The conus region was exposed. The rootlets seemed to be very thick and heavy as though they were swollen. A slightly protruding intervertebral disc was found. It did not appear to be ruptured or prolapsed in the usual manner. It was simply compressed back into the spinal canal.

for an elevation of about 3 or $3\frac{1}{2}$ mm. Through an incision in the anterior surface of the dura part of the disc was excised and part of it was curetted out. A small amount of lipiodol seemed to be held in position just above the protrusion. The rest of the lipiodol could not be evacuated by changing the patient's position.

The postoperative course was very stormy. On January 18, 1938, the blood culture was positive for hemolytic streptococci. The patient developed uncontrollable abdominal distention. Despite treatment by sulfanilamide, nasal suction and other measures, he failed to rally and died on January 20, 1938, about five months after the onset of his illness.

Pathological studies. The leptomeninges surrounding the entire cord were thickened, both membranes being about equally involved and measuring from 55 to 210 microns in thickness. The subarachnoid space was narrowed and in some areas completely obliterated. The pia-arachnoid appeared avascular, acellular and somewhat hyalinized. Not even the remnants of pyknotic nuclei could be detected. The arachnoid trabeculae were narrowed and thickened. The membranes within the commisures were also greatly involved. The sulcal arteries were completely surrounded and compressed by the thickened meninges, producing a definite vascular narrowing. Even the smaller paracentral arteries were partially compressed by the extensive meningeal changes.

The rootlets as they passed through the thickened meninges were greatly constricted and appeared to have undergone partial destruction. They showed a great decrease in the number of myelin sheaths with a secondary fibrous tissue replacement of the destroyed elements. Almost half the rootlet fibers appeared to have been replaced.

The spinal cord showed a moderate demyelination which was particularly marked in the posterior columns. The nerve cells appeared structurally intact.

Case 2. J. J. was 51 years of age at time of death, November 1940. In May of 1937, the patient first noted an itching sensation in band form at the level of the nipple line. At the time of examination, a burning and smarting sensation replaced the itching. The sensations were intermittent, coming in the form of attacks as frequently as every five or six seconds on one side or the other. Two days after the onset of the difficulty his appendix was removed at another hospital. A week after operation the right leg became numb and he experienced some difficulty in walking. In a few weeks the left lower extremity became numb. He stated that when he crossed his legs in bed he was unable to determine which leg was on top. He first entered the Hospital three months after the onset of his illness. His chief complaint was numbness and loss of sensation in the legs from the hips down to and including his feet. He also complained of a constricting sensation around his waist.

His past history and family history were essentially negative. In March 1937, the patient wrenched his back while lifting a heavy box. He was not able to work for two weeks.

Physical examination was negative except for the following-neurologic findings. The cranial nerves were essentially normal except for diminution in visual acuity on the right. He was unable to read large newsprint with the right eye. The upper extremities were normal, except that the right triceps reflex was more active than the left. Only the right upper abdominal reflex was elicited. There was spasticity of the legs, with hyperactive deep reflexes and positive Babinski sign bilaterally. There was marked weakness of the right leg. Vibratory sensibility, muscle pain and position sense were normal in the left leg but markedly impaired in the right leg. Light touch and pin prick were felt normally down to the third rib on the right and the fourth rib on the left, below these levels there was patchy loss of superficial sensation. There was no sphincter impairment.

Laboratory studies, including tests for syphilis, on the blood and spinal fluid, were negative. There was no evidence of subarachnoid block. The spinal fluid was clear and colorless, contained 40 mg of protein per cu mm, and no cells. The gold curve was 022110000.

Roentgenographic studies of the spine with the use of lipiodol were negative.

About three weeks after his hospital admission, the patient experienced some improvement. His legs improved in strength and his sensory disturbances were not so severe as previously. He was discharged in September after one month of hospitalization. However, his improvement was of brief duration, and he was readmitted in October 1937. In November 1937, a laminectomy was performed in the region of the seventh cervical and first thoracic vertebrae. There was no obstruction. The cord appeared normal. The arachnoid seemed thickened in several places. His postoperative course was uneventful and he was discharged unimproved. He was followed in the outpatient department from that time until his final hospital admission in 1940. He complained bitterly of constant itching and burning sensations. He was unable to sleep, lost weight, and gradually became weaker. He seemed to improve following a course of deep roentgen-ray, but his improvement was again of short duration. His weakness became so marked that it was necessary again to admit him to the hospital in September 1940. At that time he complained of bladder and rectal incontinence of three or four months' duration. During the last six months previous to admission it was difficult for him to walk because of weakness of the legs. He had last reported two weeks prior to admission. He first had numbness of both hands and then his left hand became paralyzed. Neurologic examination showed spastic paralysis of both legs and atrophy of the small muscles of the hands. The left hand was flexed at the wrist and the fingers were flexed in the form of a cup. Both arms showed a patchy superficial sensory loss. The patient developed signs of urinary tract infection. He became weaker, developed a pneumonic process in the right lung, and died on November 6, 1940, about three and one-half years after the onset of his illness.

Pathologic finding. Autopsy revealed a pneumonic process in the right lung. Serial sections of the brain revealed no gross abnormalities. The dura was normal except for thickening in the operative region. The arachnoid showed yellowish, thickened, indurated areas averaging about 5 mm in diameter and scattered throughout the thoracic and lumbar areas. There was atrophy of the upper thoracic and cervical regions of the spinal cord with small areas of hemorrhagic softening.

Microscopic studies showed a moderate diffuse thickening of the pia-arachnoid throughout all levels of the cord. This alteration was most marked in the pia, which measured 15 micra in thickness, was very acellular and contained very few vessels. The arachnoid was less severely involved but was also definitely thickened, especially in the anterior and posterior aspects of the cord. The extensions of these membranes into the commissures showed a similar structural alteration and thickening. The rootlets were completely surrounded by these thickened meninges but showed no structural alterations.

The sulcal arteries were for the most part uninvolved. In a few areas their lumina were narrowed. In some of the sacral segments these vessels appeared completely occluded and had produced a focal softening within the cord. Sections through the upper sacral and lower lumbar levels revealed a complete central cavitation of the cord. The tissues around this cavitation were fragmented but showed a minimal degree of cellular reaction.

The spinal cord showed a diffuse swelling of the myelin sheaths and some swelling of the anterior horn cells. Numerous distended vessels and petechiae were present throughout the gray matter of the cord.

Case 3 A. M., a white male, was 57 years of age at time of his death in August 1940

The patient was admitted to the General Hospital in January 1940, complaining of pain and weakness of the left leg, numbness and a sensation of cold in the toes and inability to walk. The symptoms began seven months previously with pain in the left ankle. In a few weeks the pain began to spread, gradually involving the calf, knee, thigh, and hip on the left side. The pain was steady, aching in character, and made worse by cold. It was noticed that his toes would readily become damp and cold. This was more marked in the left foot. Several months after the onset of the illness, the patient developed marked weakness in the left foot. For a few months prior to admission he had had urinary frequency.

Physical examination revealed a well-developed, obese white man who did not appear to be acutely ill. His feet were cyanotic and cold to the touch. The upper extremities were essentially normal. There were fibrillary tremors in both thighs and a flaccid paralysis of the left leg with absent deep reflexes and foot drop. The right leg was very weak. There were patchy scattered areas of hyperesthesia.

Laboratory studies showed a hemoglobin of 91 per cent and a white blood count of 6,050. The spinal fluid was clear and contained 50 mg per cent of protein and no cells. The pressure and response to the Queckenstedt test were normal. Air myelography was negative.

Course The patient complained constantly of pains in his legs. In May 1940, about one year after the onset of his illness, there was definite atrophy of both legs from the hips down. At that time he complained of paresthesias in both hands. In June he contracted lobar pneumonia which developed into a chronic unresolved process. In August a neurologist recorded atrophy of the muscles of the arms with marked weakness and flaccid paralysis of both legs with marked atrophy. The patient gradually became weaker, developed pneumonia on the right side, and died in August 1940, about 15 months after the onset of his illness.

Pathologic findings The spinal cord and meninges were grossly normal. The vessels at the base of the brain revealed a moderate degree of arteriosclerosis. Serial sections of the brain showed no gross abnormalities.

Microscopic sections revealed a diffuse but irregular thickening of the spinal leptomeninges, which measured from 80 to 175 micra and produced a partial obliteration of the subarachnoid space. These membranes were extremely fibrous and relatively acellular, although they did contain a few nests of mononuclear cells. The vessels surrounding the cord were markedly compressed by the thickened meninges within which they were enmeshed. Some of the vessels were almost completely occluded.

The rootlets as they passed through the involved membranes did not appear to be extensively altered although in some of the lumbar segments there did appear to be a mild compression of the posterior rootlets with some replacement of the destroyed elements by connective tissue.

The cord appeared intact, neither the white nor gray substance showing any changes.

Case 4 (This case is being reported through the courtesy of Dr A. H. Wells, Duluth.) G. H. was a male child who was 17 months of age at the time of his death in May of 1940. The patient was dead on admittance to the hospital, and there is, therefore, scant clinical information. He had been in a hospital about two months before his death. At that time it was noted on admission that the child had been sick for two weeks with fever and loss of weight. He had developed cough and dyspnea and had refused food for the last two days before admission.

The physical examination revealed râles in both lungs and extreme malnutrition. The reflexes were normal.

A physician who had attended him reported that the child developed normally until 11 months of age, when he first showed symptoms. In a short time he was unable to sit up and could not eat well. Two months before death he developed a severe bronchopneumonia. Following that illness he became very much weaker, he lay in bed, hardly moving a muscle.

Pathologic findings. The autopsy, performed three hours after death, revealed a bronchopneumonia and acute pancreatitis. Postmortem tests showed a blood sugar of 30 mg per cent, and a urea nitrogen of 47.3 mg per cent.

Microscopic sections revealed a fibrosis of the pia-arachnoid throughout the entire spinal cord. These membranes were greatly thickened, and this had resulted in a complete obliteration of the subarachnoid space. In many areas the collagenous pia-arachnoid fused imperceptibly with the dura, thus also obliterating the subdural space. The arteries surrounding the cord were compressed but not completely occluded by the meningeal involvement. The nerve rootlets were encircled but not particularly altered. The only changes seen in them were scattered areas of myelin swelling with an early formation of geometric figures due to the breakdown of the neurokeratin network.

There was a decrease in the number of nerve cells in the anterior horn, the remaining neurons being pale, fragmented or shrunken. Many ghost cells were observed. Numerous petechiae were present within the gray matter and especially near the dorsomedial cell columns. A small cystic area was encountered in the gray commissure lateral to the central canal. The white matter of the cord appeared to be intact. There was a little swelling of the myelin. This was most pronounced in the marginal region of the lateral columns.

SUMMARY

The clinical course and the autopsy findings in four cases of disseminated arachnoiditis are recorded. One case is that of a 17-month-old boy.

The roentgenographic findings following cisternal injection of lipiodol are characterized by arrest of the oil at multiple levels.

Rootlet pain over widely separated areas and evidence of anterior rootlet involvement are suggestive diagnostic features.

The rootlet involvement is due to impingement by the proliferative leptomeningitis.

The intramedullary cord changes are frequently due to vascular narrowing and occlusion, because of the proliferative perivascular reaction.

BIBLIOGRAPHY

- 1 DEMEL, R. Die Meningitis serosa circumscripta cerebialis unter den Bilde des Hirntumors und ein Beitrag zur ihrer Aetiologie, *Arch f klin Chir*, 1932, **xxx**, 561.
- 2 HORRAN, GILBERT. Generalized cisternal arachnoiditis simulating cerebellar tumor its surgical treatment and end-results, *Arch Surg*, 1924, **lx**, 95.
- 3 LILLIE, W. I. Prechusmal syndrome produced by chronic local arachnoiditis: report of three cases, *Arch Ophth*, 1940, **xxv**, 940-947.
- 4 STOOKEY, BARRY. Adhesive spinal arachnoiditis simulating spinal cord tumor, *Arch Neurol and Psychiat*, 1927, **xvii**, 151-178.
- 5 ELKINGTON, J. St. C. Meningitis serosa circumscripta spinalis (spinal arachnoiditis), *Brain*, 1936, **lxv**, 181-203.
- 6 ELSBERG, C. A. Surgical diseases of the spinal cord, 1941, Paul B Hoeber, Inc., New York.

7. MAUS⁴, THEODOR, and KRUGER, HUGO · Ueber die unter dem Bilde der Meningitis serosa circumscripta verlaufenden Kriegsschädigungen des Rückenmarkes und ihre operative Behandlung, Deutsch. Ztschr. f. Nervenli, 1918, lxi, 1-116
8. SITINSKY, HERMAN · Disseminated spinal arachnoiditis, its diagnosis and treatment with roentgen rays, Arch Neurol and Psychiat, 1936, xxxv, 1262-1279
9. MACKAY, R P · Chronic adhesive spinal arachnoiditis: a clinical and pathologic study, Jr Am Med Assoc, 1939, cxii, 802
10. BARKER, L F, and FORD, F R · Chronic arachnoiditis obliterating the spinal subarachnoid space, Jr. Am Med. Assoc, 1937, cxv, 785-786
11. SCHWARTZ, G A, and DEFRI, E M · A case of chronic adhesive spinal arachnoiditis, Am Jr Roentgenol, 1937, xlxviii, 887.
12. ROBERTSON, E G : Spinal arachnoiditis, Med Jr Australia, 1938, i, 1043-1047.
13. POLAN, C G, and BAKER, A B · Encephalo-myelo-radiculitis, Staff Meet Bull Hosp of the Univ of Minnesota, 1940, xii, 8

NEW TRENDS IN THE TREATMENT OF CHRONIC DISEASE: AN EXPERIENCE IN SPA THERAPY*

By WALTER S McCLELLAN, M D , *Saratoga Springs, N Y*

FROM the dawn of civilization man has sought relief for his physical ailments. These, at first, were mainly acute in nature owing to the dangerous life which he lived in conflict with man and beast. Chronic disease early affected civilized man as has been proved by finding changes suggestive of arthritis and vascular disease in Egyptian mummies.

As a corollary to seeking relief, man has sought for the elixir of youth, that spark which would allow him to continue with unabated vigor the activities of youth even though age be at hand. In ancient Greece, many sought the waters with this object in view. In more recent times, glandular transplants were attempted, and during the past decade many glandular extracts and other products have been studied with the hope that some preparation might alter or stop the progressive changes which are associated with aging or the development of chronic disease.

Striking advances have been made in these studies, including the development of insulin, liver extract, sex hormones and vitamins—all valuable in the relief of disabling conditions. Yet the problems of increasing chronic cardiovascular disorders and the time-robbing disabilities of rheumatic ailments still challenge our thought and study. Improved methods for preventing and treating infections which formerly took a large toll in the younger age groups have saved the lives of many thousands of people who now have reached the middle and later decades where the degenerative chronic conditions are the principal causes of disability and death.

A Are Cardiovascular and Rheumatic Ailments Increasing? There has been much discussion as to whether or not the actual morbidity rate is increasing. Sound figures on morbidity of chronic disease are hard to assemble. Many opinions regarding the occurrence of diseases affecting the heart and circulation have depended on mortality statistics. Such data do not help when one considers the large disabling group of rheumatic conditions. Rheumatism in its various forms is an infrequently reported cause of death. It is necessary in this group to rely on limited studies dealing with morbidity to arrive at an impression regarding its importance.

Simms reports¹ that the human death rate is lowest at the age of 10, approximately one death in 800 of the population. He shows that this rate increases 8 per cent each year throughout the life span. In 1936, approximately 1,300,000 deaths occurred over 10 years of age. At the 10 year rate, only 124,000 deaths would have occurred. Therefore, 90 per cent, or 1-

* Read before the American College of Physicians, Annual Meeting, St. Paul, Minnesota, April 23, 1942.

From the Medical Department of the Saratoga Spa, Saratoga Springs, N. Y.

177,000 of the total, occurred because of an increase in the death rate with age Simms considers that this depends on the underlying process of aging involving progressive alteration of the physiological function

Simms further points out that 48 per cent of the total deaths which occurred in 1938 over 10 years of age were due to conditions affecting the cardiovascular or renal system.

In studying the vital statistics of the United States for 1939,² which have recently been released by the Bureau of Census, of the Department of Commerce in Washington, a computation of the deaths due to cardiac, vascular and renal conditions shows a total of 613,160 out of 1,387,897 Therefore, 44.9 per cent of the total deaths were due to these disorders This figure differs slightly from that of Simms given above as it was calculated on total deaths rather than those above 10 years of age

In considering similar data for the State of New York, which have recently been released in the vital statistics of the United States Department of Commerce,³ it is apparent that there is an increase in the death rate from conditions associated with the vascular system In 1935 the death rate per hundred thousand population was 481.3, and in 1939 it was 519.5 The death rate for all causes fell slightly from 1141.7 in 1935 to 1122.4 in 1939

TABLE I
Death Rate of Selected Causes in United States, 1935-1939

All causes	Death Rates per 100 000				
	1939 1122.4	1938 1111.0	1937 1168.3	1936 1173.6	1935 1141.7
Intracranial lesions of vascular origin	74.0	71.9	75.6	78.9	76.3
Diseases of heart and blood vessels	375.4	359.9	356.3	347.5	325.6
Diseases of kidney (nephritis)	70.1	69.6	74.3	77.0	79.4
Total	519.5	501.4	506.2	503.4	481.3
Per Cent of Total	56.3	45.1	43.3	42.9	42.2

Another calculation from these data shows the frequency of death due to vascular disease in the later age groups, a fact which is generally known but which may not be emphasized with sufficient boldness The death rate from heart, vascular and kidney conditions represented 50 per cent or more in all age groups over 60 years In the age group from 50 to 60, it was approximately 43 per cent of the total deaths whereas in the younger age groups the proportionate number of deaths due to heart disease was much smaller

In searching for data regarding the disability produced by rheumatic conditions, one is usually referred to the survey made in Massachusetts⁴ where it appeared that the total number of patients disabled from rheumatic conditions was equal to or in excess of those disabled from heart or vascular conditions In the National Health Survey of 1935-1936,⁵ it was estimated

that rheumatic conditions affected 6,850,000 people of which 3,000,000 or more were considered to be due to arthritis alone. Rheumatic conditions are an outstanding cause of disability of a prolonged nature and of discomfort which may be well nigh unbearable.

If one looks no further than these two great groups of chronic conditions, namely cardiac, vascular and renal diseases and rheumatic ailments, there are in excess of 15,000,000 people in this country who have some de-

TABLE II
Number of Deaths, Selected Causes by Age, 1939

Years	All Causes	Intra Vas Les*	Rheu Dis Ht†	Coronary	Heart Other	Nephritis	Total	Per Cent
Totals	149 501	9 858	3 403	11 249	35,353	9,340	69 203	46.3
0-4	8,906	23	15	2	39	22	101	1.1
5-9	940	4	58	1	24	15	102	10.9
10-14	958	9	138	—	38	33	218	22.8
15-19	1,547	18	155	2	59	39	273	17.6
20-24	2,110	14	173	7	53	68	315	14.9
25-29	2,683	43	223	21	99	89	475	17.7
30-34	3,269	44	246	61	153	138	642	19.6
35-39	4,368	106	248	198	287	170	1,009	23.1
40-44	6,188	223	264	471	649	299	1,906	30.8
45-49	8,793	389	340	837	1,139	463	3,168	36.0
50-54	11,596	631	287	1,161	2,141	612	4,832	41.7
55-59	13,433	792	213	1,460	2,884	713	6,062	45.1
60-64	15,677	1,134	230	1,647	3,897	994	7,902	50.4
65-69	17,669	1,455	199	1,821	5,053	1,242	9,770	55.3
70-74	17,497	1,649	206	1,527	5,710	1,378	10,470	59.8
75-79	15,439	1,554	180	1,091	5,564	1,329	9,718	62.9
80-84	10,833	1,076	151	628	4,354	1,019	7,228	66.7
84-89	5,355	508	58	242	2,254	520	3,582	66.9
90-94	1,778	153	17	62	759	163	1,154	64.9
95-99	379	28	2	8	167	29	234	61.7
Over 100	61	5	—	—	28	5	38	62.3
Not stated	22	—	—	2	2	—	4	18.2

* Intracranial Lesions of Vascular Origin

† Rheumatic Diseases of the Heart

gree of disability from them. Of course, many are able to carry on their work and are self-supporting but large numbers are limited in their ability to support themselves and, therefore, present a large medical and social problem.

B Is This a Problem of Senescence? Information is being assembled to determine what part various factors in the problem of aging have to do with the findings presented above. Stieglitz⁶ has pointed out that gerontology may be divided into three major categories:

- (1) The biology of aging
- (2) The clinical problems of aging man
 - (a) Normal senescence and senility
 - (b) Diseases of the senescent period
- (3) The social and economic problems of aging mankind

In considering these categories, Stieglitz states that of all the diseases characteristic of later life, the cardiovascular group, including hypertensive arterial disease and arteriosclerosis, is by far the most prevalent in the senescent. He also stresses the fact that arthritis produces an immense toll of disability although its mortality is low. He points out that the maintenance of health, which is dependent on the mode of living, type of work, adequate sleep, type and character of exercise, utilization of leisure, as well as the correction of defects, is of vital importance to the aging individual. Diets are likewise essential, particularly with relation to total food volume, minerals, vitamins and fluids. He also points out the primary objective of prophylactic geriatrics is not only the prolongation of life but the insurance of greater health, vigor and usefulness for those past the meridian. Piersol and Bortz⁷ have expressed this idea in cogent terms: "It is for science not only to add years to life, but, more important, to add life to years."

C Ten Years' Spa Experience The data presented are sufficient to indicate the scope and extent of the problem of the care of chronic diseases in this country. No panacea has been discovered for the large group of individuals who suffer from either chronic cardiovascular disorders or rheumatic disability. What can the physician offer for these patients?

The author for the past 10 years has observed the influence of spa treatment on many patients suffering from cardiovascular, rheumatic, and other chronic disorders. At the Saratoga Spa, the total number of treatments given from 1932-1941 is presented in table 3. Approximately a

TABLE III

Treatments Given at the Saratoga Spa from July 1932 to June 1942

July 1932-June 1933	95,098
July 1933-June 1934	108,840
July 1934-June 1935	100,471
July 1935-June 1936	126,672
July 1936-June 1937	146,544
July 1937-June 1938	144,618
July 1938-June 1939	135,880
July 1939-June 1940	135,298
July 1940-June 1941	127,630
July 1941-March 1942	117,913
Total	1,237,964
Estimated to end of year	12,036
Treatments for 10 year period	1,250,000

million and a quarter treatments were given during this 10 year period. Owing to the large seasonal influx, it has not been possible to establish complete registration figures for the total number of patients taking these treatments. Based on a balance between the patients who stay only a few days and those who remain for the full period of three to four weeks, it is estimated that the average patient takes 10 treatments. Therefore, approxi-

mately 125,000 patients have received treatment at the Saratoga Spa during the past decade

In 1936 a survey was made of records of patients covering both the charity group at the Spa and the patients treated by private physicians and 6,315 patients were classified on the basis of their primary medical condition. The data obtained from this study are presented in table 4

TABLE IV
Classification of 6,315 Patients Treated at the Saratoga Spa

Primary Condition	Records of the Saratoga Spa 1933-36		Records of Private Physicians		Total	
	No of Patients	Per Cent	No of Patients	Per Cent	No of Patients	Per Cent
1 Heart and circulatory disorders, including variations of blood pressure	522	26.5	1,425	32.7	1,947	30.8
2 Rheumatic conditions, including arthritis, myositis, fibrositis and neuritis	714	36.4	779	17.9	1,493	23.7
3 Gastrointestinal ailments, including liver and gall-bladder	218	11.1	896	20.6	1,114	17.6
4 Nervous conditions, including both functional and organic disorders	200	10.2	333	7.7	533	8.4
5 Metabolic diseases, including diabetes, obesity, and glandular disorders	83	4.2	174	4.0	257	4.1
6 Skin diseases (non-infectious)	18	.9	115	2.6	133	2.1
7 Miscellaneous	87	4.5	112	2.6	199	3.2
8 No disease, including general debility	121	6.2	518	11.9	639	10.1
Total	1,963	100.0	4,352	100.0	6,315	100.0

Applying the data obtained in this survey to the total number of patients treated during the decade provides information on the number of patients in each group who have received treatment. Table 5 is a summary of this information.

TABLE V
Total Number of Patients, 10 Year Period, July 1932-June 1942

Primary Condition	Patients
1 Heart and circulatory disorders, including variations of blood pressure	38,500
2 Rheumatic conditions, including arthritis, myositis, fibrositis, and neuritis	29,625
3 Gastrointestinal ailments, including liver and gall bladder	22,000
4 Nervous conditions, including both functional and organic disorders	10,500
5 Metabolic diseases, including diabetes, obesity, and glandular disorders	5,125
6 Skin diseases (non-infectious)	2,625
7 Miscellaneous	4,000
8 No disease, including general debility	12,625
Total	125,000

D What are the Results Observed in the Treatment of These Patients?

Patients coming for treatment are advised to have one of the physicians in private practice outline the program while here. Medical care is provided for patients in the charity group. Physicians in private practice contribute time to the Clinic Service during the summer months. It has not been possible to assemble at a central point records of all patients taking treatment at the Saratoga Spa. Also, many have remained only a few days and, therefore, cannot be included in evaluating the results of treatment. In summarizing the results it will be necessary to quote from individual studies which have been made on representative groups of patients. The evaluation of the results of this treatment naturally depends also on the patient's progress after he returns to his home. These data are not available except in a relatively small group of the patients who return for treatment during a subsequent season.

In studying the response of the circulation to the naturally carbonated mineral baths of the Saratoga Spa, McClellan, Joslin and Maguire⁸ reported in 1934 on the study of 102 patients, 41 male and 61 female, in whom the pulse rate and blood pressure were observed daily before and after the bath for the period of their treatment. Care was taken to allow the patient on coming to the bath house to rest for a period of 15 to 30 minutes until the pulse rate and blood pressure reached a constant level. Under these conditions it was found that the pulse rate of a large proportion of the patients reached a resting level between 65 and 75. Even under these conditions, 83 showed a reduction in the rate of the pulse after the bath, 17 showed no change, and in only two patients was there an appreciable rise in the pulse rate. When the pulse rate at the beginning and end of the cure period was compared, there was relatively little variation because, as noted above, most of these patients had pulse rates within the normal range at the beginning of the cure.

With reference to blood pressure, the records of 88 patients in the series were available for study. Of this group, 52 had initial blood pressures above 150 systolic. When the entire group was considered, the average changes from the resting level before the bath showed relatively little change. However, a more careful analysis of those patients whose blood pressures were elevated above 150 mm Hg showed that 52 per cent demonstrated a change of more than 10 mm Hg which was taken as a significant variation. The authors concluded that the response with definite changes in the level of the blood pressure was found in those patients in whom some nervous influence could account for the elevation. When definite sclerosis of the arteries was present, or when kidney changes were evident, the elevated blood pressure showed relatively little reduction as a result of the course of treatment. They noted, however, that even though the change in blood pressure was not marked, many of these patients experienced definite symptomatic relief and left at the end of their cure apparently in better physical condition.

In another study Dorrance and McClellan⁹ observed with the Tykos Sphygmomanometer 44 patients in whom the pulse amplitude and blood pressure were determined in a series of tracings, including the upper arm, lower arm, and lower leg before and after the mineral water bath. Ninety pairs of tracings were compared. In all but one patient there was a decrease in pulse rate which was typical as noted in previous studies. The blood pressure variation in this group showed approximately the same percentage of response as reported in the preceding section. Significant variations in pulse amplitude as determined by the height of the tracings were noted in a considerable number of these patients. The definite tendency toward increase in amplitude following the bath was more evident in the upper extremity than in the tracings made on the lower leg, and was also more striking when the comparisons were made of those patients in whom the amplitude in the lower leg was 2° or less. The increase in amplitude was more frequently noted if there was some initial constriction in the arterial tree. Constriction of this type may be due either to organic changes or to muscular spasm, or both. Where definite increase in the amplitude occurred, it would appear that muscular spasm was a definite factor as the change was less marked in those patients with obvious organic arteriosclerosis.

Stein and Weinstein¹⁰ have recently reported that local carbon dioxide baths prepared by chemical generation of carbon dioxide in the water did increase blood flow in the extremities as indicated by a study of the skin capillaries, the surface temperature and plethysmographic measurements.

Clinical studies include a series of careful observations by Comstock, Hunt and Hayden¹¹ on 107 patients in whom the diagnosis of coronary disease had been made. In a considerable proportion of this group, one or more attacks of coronary thrombosis had occurred. The authors reported that in 96 of the 107 patients, material improvement was noted. This is based on increase in exercise tolerance and diminution in the number and degree of anginal attacks during the period of observation. In 13 of these the improvement was sufficiently marked to include them in a separate group. The observations on the 11 patients who showed no improvement indicated that two did not complete the regime, three had advanced myocardial damage, one had suffered from malignant hypertension for three years, one was senile, one suffered from luetic cirrhosis of the liver, and one having repeated anginal attacks would not cooperate with the program. In spite of these facts two of this group reported improvement after returning home. With reference to their study of the roentgen-ray examinations, electrocardiograms and vital capacity, the authors stated that there was no marked change in the heart shadow as determined by the cardiothoracic ratio at the end of the treatment. In the electrocardiogram they noted T-wave improvement, which they described in no instance as striking, in 22 patients. There was a reduction in the P-R interval in 15 patients. The QRS complex showed no significant change. They found no material change in the vital capacity of the series of patients studied.

McClellan¹² in 1937 presented a review of the physiological studies of the carbon dioxide bath. In general the observers have found that the physiological effects of these baths include a decrease in the pulse rate, an increase in the pulse pressure dependent mainly on the drop of the diastolic, the better emptying of the venous circulation, peripheral hyperemia with increased capillary circulation in the skin, a slightly elevated minute volume output of the heart, an increase in respiration, and the elimination of large quantities of carbon dioxide from the lungs.

The author pointed out that circulatory patients with mild to moderate myocardial weakening represent suitable indications for this program of treatment. Also, the patients with coronary sclerosis including the angina of effort, generally respond to the program. In the treatment of vasospastic conditions, with changes in the peripheral circulation, the bath is indicated as relaxation is frequently obtained during and after its use.

Definite contraindications to their use cover any cardiac patient with fever or active infection. Patients with aortic regurgitation and aortic aneurysm generally show little benefit. Patients with advanced myocardial failure who require strict bed rest are not suitable for spa treatment.

In considering the results of treatment in other types of chronic diseases, the author¹³ has reviewed the regimen with reference to rheumatic conditions. Many patients with osteoarthritis, as well as nearly all patients with fibrositis or myositis will show improvement with the regimen of treatment at the Spa. Patients with rheumatoid arthritis in the acute or active stage generally do not respond well to this treatment. Here the program includes the warmer baths with the local application of either hot mineral water or mud compresses, radiant heat or the infra red lamp, and it may include exercises and massage. For the rheumatic patient, this program offers considerable promise of relief, although it can in no sense be considered as the only form of treatment which should be used for these patients. It can be applied in conjunction with the general regimen now widely approved for these disabling disorders. In observing these patients during the cure régime, results obtained include a decrease in the swelling and increase in the range of motion of the affected joints. There is an improvement in the general physical condition of the patient which is manifested by better color of the skin, better elimination through the intestinal tract and kidneys, and a better attitude toward the disability which is present.

Convalescent care which has received considerable attention during the past few years can be satisfactorily associated with a spa program of treatment. Comstock¹⁴ outlined this phase of spa work at the 1939 Conference on Convalescence at the New York Academy of Medicine. Callahan¹⁵ has reviewed similar data with reference to the convalescent patient. They point out that a proper program of convalescent care in many of the disabling conditions is of real value in their continued well-being and from the standpoint of preventive medicine it may result in delaying the progressive development of the condition. Convalescent care also is applicable in the

building-up period after the occurrence of debilitating infection or a weakening surgical operation

SUMMARY AND CONCLUSIONS

1 Chronic disease in middle and old age is a serious medical problem in this country

2 Lack of attention to matters of health in earlier years may be one contributing factor to the development of these chronic conditions in the older age groups

3 No magic drug or miraculous fountain of youth has been discovered for these conditions

4 Much investigation in the field of geriatrics is under way and it is hoped that this will be productive of information which will aid in the regulation and control of these conditions

5 Spa therapy can be utilized to advantage for selected patients with chronic ailments such as cardiovascular, rheumatic, gastrointestinal, metabolic, and skin disorders. It can be fitted into the physician's schedule for the chronic patient but he must know its indications and contraindications

6 The facilities available at the spas can also be used in the convalescent care required after acute illness or injury. Thus they have their place in the field of industrial and military medicine

7 In addition to the use of the natural agents which is the keystone of the program, rest, regulated exercise, diet control and proper recreation all have a part to play in producing the desired mental and physical relaxation

8 In order for the patient suffering from chronic disorders to derive the maximum benefit, it is necessary for the home physician to select the proper spa for his patient, taking into account the natural facilities available, the climatic factors and the availability of adequate medical control

9 Long-term observation of groups of patients with chronic diseases, who have received treatment at spas will be required to determine finally how completely effective the program may be

BIBLIOGRAPHY

- 1 SIMMS, H. S. The problems of aging and of vascular disease, *Science*, 1942, **xcv**, 183
- 2 Bureau of the Census, Department of Commerce, Washington. Deaths from each cause United States 1939, *Vital Statistics—Special Reports* 1941, **xii**, 241-247
- 3 Bureau of the Census, Department of Commerce, Washington. New York—Summary of Vital Statistics, 1939, 1941, **v**, 837-869
- 4 BIGELOW, G. H., and LOWBARD, H. L. Massachusetts Survey of Chronic Diseases New England Jr Med 1930, **ccm**, 1232
- 5 National Institute of Health U. S. Public Health Service. The National Health Survey, 1935-36
- 6 STIGLITZ, E. J. Problems of aging, *Pennsylvania Med Jr* 1941, **xl**, 211
- 7 PIERSON, G. M. and BOKTZ, E. I. Aging process medical-social problems. *A. J. Med*, 1939 **xxvii**, 964

- 8 McCLELLAN, W. S., JOSHIN, E. R., and MAGUIRE, G. V. The influence of natural carbonated mineral water baths on blood pressure and pulse rates, *New York State Jr Med*, 1934, **xxxv**, 101.
- 9 DORRANCE, S., and McCLELLAN, W. S. Effect of natural carbonated baths on rate and amplitude of pulse and blood pressure, *Arch Phys Therap*, 1940, **xvi**, 133-139
- 10 STEIN, I. D., and WEINSTEIN, I. The value of carbon dioxide baths in the treatment of peripheral disease and allied conditions, *Am Heart Jr.*, 1942, **xviii**, 349
- 11 COMSTOCK, C. R., HUNT, H. D., and HAYMAN, R. S. The value of a "cure régime" in the treatment of coronary disease, *New York State Jr Med*, 1935, **xxxv**, 715
- 12 McCLELLAN, W. S. The place of carbon dioxide baths in the treatment of diseases of the circulation, *Internat Clin*, 1937, **i**, 199
- 13 McCLELLAN, W. S. The Saratoga Spa—its place in the treatment of rheumatic disorders, *Arch Phys Therap*, 1937, **xviii**, 408-473
14. COMSTOCK, C. R. Convalescence in coronary disease with special reference to Saratoga Spa, *Bull New York Acad Med*, 1940, **xvi**, 546-549
- 15 CAHILLAN, E. J. Convalescent care at the Saratoga Spa, *New York State Jr Med*, 1941, **xli**, 604

CIRCULATORY DISTURBANCES IN PROSTATIC HYPERTROPHY ~

By MEREDITH MALLORY, M D , F A C P , FRED MATHERS, M D , F A C P ,
LOUIS M ORR II, M D , F A C S , and PALMER R KUNDERT,
M D , F A C S , *Orlando, Florida*

A REVIEW of the medical literature reveals the fact that but little consideration has been given the very important relationship of the hypertrophied prostate to circulatory disturbances. Perhaps it has been assumed that persons of the age to have hypertrophied prostates should have certain cardiac and circulatory changes as a natural sequence of old age. As we live in a section of the country which has a large influx of elderly people during a portion of the year, the opportunity of observing the diseases of advanced years is greater. Also, owing to the fact that people from nearly every part of the country are here at least a short while, methods of treatment in other sections can be clearly observed.

To the majority of diagnosticians, the patient with the cardiovascular-renal syndrome still represents a poor surgical risk. Operation is often deferred or, in many instances, abandoned completely because of the chances involved, with the result that a large percentage of patients with prostatic disease are denied timely relief through surgery because of the co-existing cardiovascular disturbance. After establishing the cardiac functional capacity or incapacity of the patient, a great number of urologists feel that, in cases of advanced myocardial incompetence, suprapubic cystostomy or catheterization should be resorted to as the only means of relieving the urinary obstruction.

There is no question but that there is a general tendency to treat prostatic hypertrophy too conservatively because of the existing evidence of some degree of circulatory failure. The next question is whether or not the circulatory disturbances are the result of, or at least aggravated by, the presence of an incompletely emptied bladder. It would seem that either the retention of nitrogenous products in the blood stream or some reflex action upon the excretory function of the renal units has a definite effect upon the circulatory system. Campbell¹ advances the theory that hypertension occurs in a small group of prostatic patients because of the inability of the upper urinary tract to dilate owing to an anatomic factor, usually an intrarenal pelvis, and he points out the strikingly low rate of hypertension (19 cases) among the group of 173 cases of prostatism studied by him.

The final decision as to surgical intervention depends, in many instances, on the condition of the heart and vessels. The responsibility is left by many urologists upon the shoulders of the internist or cardiologist, and too often

* Presented at the Annual Meeting of the American College of Physicians, April 21, 1942, St Paul, Minnesota

the opinion is that the patient is not able to undergo surgical interference. Many allow their patients to die with their hypertrophied prostates rather than take the risk of removing the obstruction which, in practically all cases, will help to improve the circulation. This fact can be effectively demonstrated by doing suprapubic drainage on the very poor right before attempting resection or even prostatectomy.

No definite criteria or rules as yet can be laid down relative to the laboratory procedure which would indicate when it is safe to proceed. The decision must be based largely upon the clinical judgment of those who have had the opportunity of studying many cases. Laboratory findings and functional tests are empirical at best, and it is impossible to formulate any one into any safe rule which could be followed. As an example, in the series of patients to be presented the blood urea nitrogen varied from a low of 10 to a high of 31 milligrams which is certainly no evidence of impending danger. The blood pressures ranged from a systolic of 70 mm Hg and a diastolic of 50 to a systolic of 220 and a diastolic of 110.

That the inter-relationship between renal dysfunction and cardiac impairment is clearly recognized is shown by Thompson. In a study of a large series of patients subjected to prostatic surgery, recognized heart disease was found in 23 per cent on admission and 28 per cent showed blood pressure readings above 160 millimeters mercury.

Among the cardiac symptoms complicating the prostatic hypertrophy were auricular flutter, auricular fibrillation, myocardial hypertrophy, rheumatic heart disease, angina pectoris, and hypertension. These patients ranged from 65 to 80 years of age. Forty-eight per cent had a systolic blood pressure above 150 and the average blood pressure in this group was 179.5 systolic and 100 diastolic. On discharge from the hospital after relief of the prostatic obstruction the average blood pressure had fallen to a systolic of 140 and a diastolic of 80.

Preoperative strengthening of the myocardial reserve is the essential step in lessening the hazards of major surgery. The failing heart muscle in the case of prostatic obstruction should be treated as any other case of cardiac failure. Complete rest is the most important therapeutic agent and with this must be relief from frequent or difficult passing of urine. Digitalization should be begun at once and continued until after the shock of the operation is over. As many of these cases show some degree of avitaminosis, the administration of vitamin B complex is strongly advocated. This is better done by the intravenous injection. Anemia is present in many cases and should be treated during the preoperative period. The preoperative period must not be curtailed or hurried.

Elevation of blood pressure should not constitute a contraindication to surgery. Wilhelm³ has recorded the case of one patient with a systolic blood pressure of 240 who had four resections without reaction at any time, and another with hemiplegia and a systolic pressure of 210 who underwent two resections with no ill effects. Although Seng⁴ stresses the pos-

sibility of any catastrophe occurring in the hypertensive prostatic patient because of the condition of his cardiovascular system, he, as well as O'Connor⁵ and others, has demonstrated the marked fall of blood pressure following the relief of chronic urinary retention. O'Connor recorded that the blood pressure in 75 per cent of hypertensive patients reached its lowest level in 48 hours after the institution of continuous catheter drainage.

Cutler⁶ stresses the point of preoperative study and care of patients in general, and emphasizes that the elderly will always require a longer period of preoperative observation and a more accurate study of end results than other groups. In connection with this Cutler states: "The ideal considerations surrounding a satisfactory surgical risk permit the patient to come to operation with the tissues adequately supplied with fluid, the food reserves in their normal state, the metabolism adjusted as perfectly as it may be, the intestines working normally, the circulation at its optimum level, and a nervous system as undisturbed and peaceful as in daily life."

Levine⁷ enumerates a series of surgical patients suffering from various types of heart disease. In the group with marked valvular disease only 2.1 per cent of the deaths followed the surgical procedure, whereas among the patients who showed non-valvular cardiac involvement (hypertension, chronic myocarditis, etc.) there was a mortality rate of 4.9 per cent.

Mortality rates as shown by one of us* vary with the experiences of the operator. It was noted that five urologists, who had operated upon more than 500 cases each, had a combined mortality of 1.9 per cent in 4,767, whereas 25 who had done between 100 and 200 resections had a combined mortality of 4.1 per cent in 3,530 cases. It is obvious, therefore, that morbidity as well as mortality have been greatly lessened by the experienced resectionist. Immediate postoperative shock has been practically eliminated and many patients who represent a surgical risk may at present be given timely relief from their distress.

Thompson and Habern⁸ claim that the choice of transurethral prostatic resection has materially reduced the immediate postoperative mortality rate, formerly encountered as a result of suprapubic and perineal prostatectomies, by 90 per cent. Even patients belonging to the advanced age groups, who suffer from serious cardiovascular-renal disease and other degenerative impairments, tolerate this form of surgery without ill effects. These two authors have also analyzed the histories of 1200 patients 70 years old or more, who were operated upon prior to January 1, 1938. Some of these surgical candidates had submitted to two, and in a few instances to three operations, making a total of 1,361 transurethral resections.

In comparison with the figures quoted above, which include all surgical patients, 29 cases have been selected that give either a history of acute myocardial failure or a history of recent myocardial infarction. All were advised to have surgical interference for their urological condition. The degree of cardiac involvement varied but as a whole they were those cases

Dr. Louis M. Orr II.

that are very often advised not to undergo surgery. Two of these patients had had coronary occlusion but had recovered. The remainder all had signs of a failing myocardium and in some there was a history of previous attacks going back one to eight years.

The ages of the patients in this series varied from 55 to 83, the average age being 71 years. Of this series seven have died, i.e., a percentage of 24.1. One died one year after the operation. Another died seven months after surgical interference and the urological condition of this patient was complicated by diabetes mellitus and, previous to the operation, by the presence of a bundle branch block which later disappeared. There was a period of fair circulatory balance following the operation, however, the seriousness of his condition could not be impressed upon him and a few months following operation a long motor trip was undertaken which brought on circulatory failure for which no relief could be given. A third patient died three months after leaving the hospital. He was uncooperative even in the hospital and after returning to his home in a neighboring county no supervision was possible. Two died of circulatory failure the day following resection, and another death occurred in the case of a diabetic whose blood sugar could not be controlled following operation and who presented considerable liver damage. The seventh died of bronchopneumonia five days after the resection.

After taking into consideration the various complications, it can be said that only two patients who had signs of circulatory failure previous to admission actually became worse immediately following the operation. One of them had suffered from bronchiectasis for a number of years. This is a percentage of 6.8 which is only three to four times the mortality record of all cases considered in the various series presented. The patients of this series definitely belong to the class which undoubtedly would have succumbed early to circulatory failure had they not been given a chance for a little borrowed time through surgical interference.

Hypertension was present in eight cases previous to the operation and on discharge from the hospital the pressure was within normal limits. In the 29 cases the average length of stay in the hospital before any surgical procedure was undertaken was 11.5 days. The average postoperative stay at the hospital was 10.4 days, with an average total of 21.9 days of hospitalization. Of this series four patients had suprapubic prostatectomies, and two others had suprapubic prostatectomies following resection.

In only four cases were the laboratory data indicative of a nitrogen retention, so that this factor can be eliminated as a cause of failing circulation. An important factor which is seldom mentioned is the stress and strain associated with the frequency and marked exertion during urination. This straining must be a definite factor in the circulatory failure for it will be noticed that a cystotomy or an indwelling catheter will usually bring on more or less relief to the heart muscle. Bed rest was not the factor that was necessary for the cardiac improvement for many of these patients were not

confined absolutely to bed. It can definitely be said that all except those mentioned showed great improvement following their operation.

The following case may serve as a concrete example. This patient was seen in 1935 at the age of 63, when examination revealed myocardial damage. He was in bed for several weeks and was seen in consultation by two internists who both considered him to be near the end. He was treated intermittently, in 1937 an electrocardiogram showed coronary sclerosis had developed, and in 1938 a posterior coronary occlusion with accompanying muscle damage complicated the clinical picture. The patient also had trouble with urinary retention. By 1940 he had dropped all work and activities owing to his aggravated heart condition and he began to complain of difficulty in emptying the bladder in the morning. There was no increased frequency during the day. The patient was finally admitted to the hospital in October, 1940. At the time of his admission he complained of increased urinary difficulty. Physical examination revealed an enlarged prostate, a moderately enlarged heart with a soft blowing systolic murmur at the apex. Blood pressure was 110 mm Hg systolic and 70 mm diastolic. An electrocardiogram showed myocardial damage, extra-ventricular systoles, coronary sclerosis and a posterior infarction.

The operative procedure was carried out under local anesthesia (spinal pontocaine) and consisted of bilateral vas ligation and prostatic resection, both manipulations requiring a total of 50 minutes. Approximately 11 grams of tissue were removed. A No. 24 Foley catheter was used. Complete and final diagnosis in the case of this patient was carcinoma of the prostate, arteriosclerotic heart disease, coronary sclerosis and occlusion with mitral insufficiency. Regardless of these four serious complications the patient stood the operation remarkably well and made an uneventful recovery. He was allowed out of bed on the fourth postoperative day and was dismissed on the ninth day after surgical intervention. He has returned to his normal activities and periodic examinations have revealed no complications of any kind. Thus, as well as the majority of patients who had cardiovascular complications and were subjected to prostatic surgery, showed decided and most remarkable improvement of all clinical symptoms. Normal function of the circulatory system was restored as soon as the obstruction caused by the hypertrophied prostate was removed.

The choice of a proper anesthetic is of primary importance in the surgical treatment of these patients. It should be easy of induction, provide adequate pain relief, be rapidly eliminated from the body and reduce gastrointestinal, pulmonary, and circulatory complications to a minimum. Although the ideal anesthetic has not as yet been discovered, it is felt that pentothal sodium given in conjunction with oxygen and administered by a capable anesthetist most clearly satisfies these requirements for the cardiac case.

Infusions of plasma or whole blood should be a part of the routine postoperative treatment in severe cases. The most speedy and skillful per-

formed operative manipulation fails to avoid a serious loss of blood which must be replaced promptly if shock is to be eliminated. It is probable that the loss of blood will average in the neighborhood of 300 to 400 cc. According to Gundersen¹⁰ 70 per cent of his patients who were studied in 1937 received one or more blood transfusions. In these cases heart disease claimed only two patients one year after leaving the hospital.

An attempt has here been made to evaluate the favorable and unfavorable conditions associated with obstructing prostatism and to determine the advisability of prompt surgical interference in spite of an impaired cardiovascular system. It is a fact that prostatic patients of the old age group who several years ago would have been rejected as too great surgical risks because of advanced senility or serious cardiac defects, are today being treated by means of resection with excellent postoperative results and, as has been shown herewith, decided improvement of the failing heart muscle. Mortality rates in prostatic surgery can and will be greatly lessened by a careful surgical approach to the problem which must be based upon preliminary preparation of the patient.

SUMMARY

1 Cases of hypertrophied prostates showing signs of active circulatory failure are, generally speaking, to be considered fair surgical risks.

2 The removal of the obstruction to the urinary outflow aids greatly in the improvement of the cardiac condition. The exact reason for this is as yet unknown.

3 Failure to operate on these cases only aggravates the condition of the heart.

4 Proper preoperative and postoperative treatment will result in a reduction of the mortality rate to a level comparable with the most favored surgical risks.

BIBLIOGRAPHY

- 1 CAMPBELL, E. W. Significance of hypertension in prostatics with chronic urinary retention, *Jr Urol*, 1941, xlv, 70-81.
- 2 THOMPSON, G. J. Clinical data concerning prostatic resection, *Jr Urol*, 1938, xl, 121.
- 3 WILHELM, O. J. Refinements in technique imperative for successful transurethral prostatectomy, *Jr Urol*, 1941, xlv, 612-621.
- 4 SENG, M. I. Study of blood pressure in prostatism including cardiovascular changes, *Jr Urol*, 1931, xxv, 313.
- 5 O'CONOR, V. S. Further observations on blood pressure in cardiovascular changes, *Jr Urol*, 1923, x, 135.
- 6 CUTLER, E. C. Selection of patients for surgery, *Rhode Island Med Jr*, 1939, xxii, 147-152.
- 7 LEVINE, S. A. Clinical heart disease, 1936, W. B. Saunders Company, Philadelphia and London.
- 8 ORR, L. M., II. Present day views on prostatic obstruction, *Jr Urol*, 1937, xxxvii, 28.
- 9 THOMPSON, G. J., and HABEIN, H. C. Transurethral prostatic resection, review of 1200 cases of patients more than seventy years old, *Am Jr Surg*, 1939, xlv, 27-32.
- 10 GUNDERSEN, A. H. Management of prostatic disease in persons past seventy-five. Report of seventy-five cases with end results, *Jr Am Med Assoc*, 1939, cxii, 833-835.

SOME PROBATIVE ASPECTS OF THE EARLY GERMANIC CODES, CAROLINA AND BAMBERGENSIS *

By SAMUEL POLSKY and SPENCER BERESFORD,†
Cambridge, Massachusetts

IN FEBRUARY 1533, a document of unique historical importance was struck on the press of Ivo Schoffer, a printer of Mainz. As though foreshadowing its ultimate obscurity in English speaking countries, this prototype of scientific-legal proof was indifferently received and inattentively handled from its inception.¹ Enacted as a statute a year earlier by the Reichstag at Regensburg under the imposing title, "Kaiser Karls des funfften und des heyligen romischen Reiches peinlich Gerichtsordnung" it is perhaps better known as the Carolina Code, or the Penal Laws of Chas V.²

Earlier in the 1500's had appeared another code, the Bambergensis. This work, composed in large measure by Johann Freiherr von Schwarzenburg, served as a model and foundation of the criminal law of Germany for approximately four centuries. That it profoundly influenced the Carolina Code is patent from the striking similarities in form and content between them. Article CXLVII of the Carolina Code is, for example paralleled almost word for word by Article CLXXIII of the Bamberger Code.³ In geographic scope, however, the Carolina was by far the broader code. Its jurisdictional effect was nationwide, whereas the Bambergensis (and also the Brandenburg code) represented local law only.

I Anglo-Saxon Underestimation of the Codes' Significance. The neglect of both these tracts in the English-speaking world during the past century may be attributed in part to the disproportionate harshness of the system of punishments they expostulate. The rude community life of renaissance Europe did not regard burning, drawing and quartering, breaking on

* Received for publication March 9 1943

† Research Students Harvard Law School Cambridge, Mass. Mr Beresford is now an Ensign in the Naval Forces of the United States

¹ Von Bar, *History of Continental Criminal Law* (1916), p. 44 points out that not a single copy of the original was retained by the imperial officials and that there are enough errors in the writing and editorial work of the original draft as well as in the typography of the principal edition of February 1533 so that frequently it is difficult to ascertain the meaning. There is also, according to that authority, some dispute as to the existence of earlier editions.

- *Constitutio Criminalis Carolina* ed. I. F. Ludovic Halle 1716. Further references to this code are by way of our own translation from the original German.

² Article CXLVII of the Penal Laws (Carolina Code) and Article CLXXIII of the Bamberger Code are identical except for (1) punctuation and spelling, the Bamberger Code being written apparently in older German; (2) the addition in the Penal Laws of the words "und the fricas" ("and Rumor") after the word "blow" and before the words "and how he lived after he was struck;" and (3) the more formal ending of the Article in the Penal Laws which concludes "and the judge shall, in accordance with his order, see that the law, and the authorities and purpose of the law and the purpose of the article are taken into consideration to such testimony."

the wheel or rack, pinching with hot tongs, or burying alive as particularly inhuman or barbaric. It is not surprising, therefore, to find such punishments incorporated in both codes. These codes were intended as treatises limning the law as they found it, with the greatest degree of clarity possible, rather than statutes of legislative reform. Nor is it strange that the same cruelties were reflected in the use of torture as a means for determining the truth.

It is not difficult to overlook primitive methods of punishment in a work not primarily concerned with penal reform nor with modifications in the severity of corporal punishment. Such leniency cannot be condoned when these same tortures are a matter of procedure in an exposition chiefly procedural and concerned with rules of proof. Perhaps this fact has blinded able legal historians to the full importance of the Carolina and Bambergensis as almost aboriginal harbingers of an era of scientific-proofmaking of which only the van has arrived even today. External evidence had already contrived even at that early age to influence that least objective of all probative tests, the rack. Thus Article LIX of the Penal Laws (Chas V) and Article LXXII of the Bamberger Code provide in identical language for excusing a defendant from torture (the rack) so long as he has dangerous wounds or bodily injuries.⁴

In the interval between promulgation of the Bambergensis and the Carolina, the former code had already achieved recognition as authoritative. Thus in 1516 it was adopted with relatively few changes as the code of the margravate of Brandenburg. By the time of the Carolina, the strong sympathy of the earlier codes toward objective evidence in the form of expert testimony had sufficiently permeated legal thought so that express provisions of this character were added where none had expressly existed before. Thus, for example, we find no section in either the Bamberger or Brandenburg code to parallel Article CXLIX of the Penal Laws (Carolina), "of the Inspection of the Body of a Slain Man Before Burial."

Where there is reason to believe that there has been foul play, the judge shall have the clerk of the court and one or more surgeons carefully inspect the dead body before burial, and carefully observe and record all the wounds, bruises and swellings that they find.⁵

⁴ The Note to Article LIX says that epileptics are a hard problem, and cites Brunnem, *proc inquis*, c 8 membr 5 n 28 seq, to the effect that the opinion of a physician should be consulted before judgment is given, and that the judgment should conform to the physician's opinion as to what kinds of torment, if any, the men are subject to, and also cites Carpozov, *prav crim qu* 118 num 18 and 19, to the effect that physicians should be consulted as to whether epilepsy is really present or the fits are simulated.

⁵ The Note to Article CXLIX conjectures that the inspection need not be made in the presence of the judge. It adds that the corpse may sometimes be exhumed, if it was buried without previous inspection and putrefaction has not yet set in.

Citation of B Stryk, *de jur sens diss*, 1 c 2 num 34, who wrote that surgeons were altogether prohibited from exploring a wound, before the cadaver had been dissected, with any kind of iron instrument, and from probing or cutting any interior part of the body. The reason given was the censure of physicians who were summoned to inspect corpses on which surgeons had already worked with iron instruments. For the more surgeons tamper with the bodies, the less the physicians themselves can draw inferences from their inspections.

II Evaluation of the Codes It must not be imagined that the Carolina, and, a fortiori, the earlier codes, are in any sense a complete and objectively consistent system of scientific proof. Even in their most detailed sections concerning the elements of objective proof-making, important girders are missing in the superstructure of evidence. These gaps may be traced, however, to philosophical inadequacies rather than fallacies in logic. The Code Carolina is internally harmonious with respect to its reasoning. Its deficiencies are philosophically and psychologically inherent in the culture of its period, a period that believed that the only positive proof of crime was confession⁶ and that torture was merely an instrument of confession. Although sections LXIX and XXII of the Carolina prohibited any conviction upon circumstantial evidence, judicial interpretation soon limited the prohibition to the graver offenses. And even here the technical requirements of confession or eye-witness testimony were speedily ignored. Where the judge was convinced of the actual guilt of the defendant, he sentenced him to *Veidachstrafe* ("extraordinary" or as later known, "suspicion" punishment). The lay feeling against external or circumstantial evidence, uncorroborated by confession or eye-witness testimony, merely shifted the method whereby the ultimate end was achieved. The judiciary which recognized the value of circumstantial proof assumed the power to effectuate and express that recognition in punishment, despite the provisions of the Carolina. Seen in proper perspective the Carolina channelized much of the incipient law of scientific proof, but was itself only a part of a much broader stream flowing in the same direction.

III Comparative Analysis of the Codes Comparative analysis of a particular problem in probative valuation in both codes may more readily illustrate their differences and salient strengths. Particularly apt are Article XXXVI of the Penal Laws (Carolina Code) and Article XLIV of the Bamberger Code concerning the proof-standard for maternal infanticide. The earlier (Bamberger) code provided

But if the baby has been killed so recently that the milk in the breasts of the mother may not yet be gone,

and the woman who is blamed asserts that she is a virgin

then her breasts shall be milked, and if milk is found in the breasts she must necessarily have had a child and shall be put to the torture (for questioning)

In the asset column of the code may be listed the clear formulation of a test in language simple enough for the lay mind to grasp, and the execution of the test by those especially qualified to attest the significance of the results, as well as the results themselves. As undeniable weakness of the article, on the other hand, is the rigidity of the test not making allowances for possible differences of medical opinion. The Carolina Code corrects this obvious de-

⁶ See von Bar, *History of Continental Criminal Law* (1916) p. 52. Also the prejudice of the lay mind of today toward circumstantial evidence as the sole basis of conviction in capital crimes.

fect by changing the absolute conclusion of the law to a strong presumption rebuttable by sufficient weight of expert testimony. A glance at the Penal Laws of Chas. V strikingly reveals the difference.

If the baby has been killed so recently that the milk in the breasts of the mother may not yet be gone, then her breasts may be milked, and if milk is found to come readily from her breasts, there is a strong presumption against her that she should be questioned under torture. But since several court physicians say that from various natural causes a woman who has borne no child may have milk in her breasts, therefore when a woman in this situation tries to excuse herself accordingly, further experience, that of midwives and others, shall be consulted.⁷

Had the early Germanic codes rested their case at this point, their conceptual similarity to the spirit of the modern idea of scientific proof-making would have been even more striking. Unfortunately, in the serious crimes, circumstantial evidence alone was considered insufficient. As has been pointed out before, the judiciary frequently by-passed this hurdle through "suspicion" punishment (i.e., punishment based on sufficient circumstantial data to satisfy the judge of the actual guilt of the accused, despite lack of a confession or eye-witnesses). Still, the codes themselves are undeniably weakened as models, even early models, of the law of proof by such provisions as Article XXXV of the Penal Laws, and Article XLIII of the Bamberger Code. These articles concern the circumstances on suspicion of infanticide. Yet even here the directional urge toward scientific standardization is manifest, at least to the extent of determining the primary issue of still birth versus death after birth. The *Note* to the articles mentioned, asks

What shall be done when an infant is found killed?

The question whether the infant was born alive is submitted to medical opinion.

First examine the lungs to see if they are red and bright, and throw them without bruising into a kettle of water, then if they *float*, "that is a certain and infallible sign of a child born alive, according to the opinion of all physicians and anatomists" (Authorities cited). If, on the contrary, the lungs *sink*, that is a sure sign that the foetus was dead in the womb, and never breathed.⁸

⁷ The *Note* remarks that no appeal to expert evidence is provided for in either the Bamberger or the Brandenburg Code, since at the time when they were formulated the milking test was considered infallible. Considering the close spacing of the various codes (Bamberger 1507, Brandenburg 1516, Carolina 1530-32), this explanation with respect to the omission may be open to some question. But even if accepted at face value the importance of the procedural difference between the earlier codes and the Carolina remains unaltered from the standpoint of objective standards of expert testimony.

⁸ Pp. 50-51. The note then refers to a commentator, B. Beyer, who pointed out that the test works well with a fresh cadaver, but not with a cadaver that has had time to putrefy, since putrefaction generates gas. See, also, Article CLXXXIX which provides for insanity to be taken into account in fixing the punishment for crime and specifies that expert witnesses may be heard on that issue. In the note to this article a case is reported where the verdict of the court in a case of alleged mental irresponsibility was based upon the expert opinion rendered by the Medical Faculty of the University of Halle (1706).

Article CXLVII, of the Penal Laws, although not specifically concerned with infanticide, embraces that problem under the general heading, "When someone has been struck, and dies, and there is doubt whether he has died of the wounds" In such a case, the parties may introduce the testimony of the attending surgeon, and of other persons familiar with the facts, as to whether the deceased remained standing after the blow, and how long he lived after he was struck, and the judge shall give due consideration to such testimony The important factor to be noted is that the medical inferences of the attending surgeons are placed on the same plane with the testimony of other persons familiar with the facts That this is due to a clearly defined regard for principles of scientific proof and not a cultist psychology of science-worship is evidenced by the *Note* to the Article This *Note* "informs us that surgeons by themselves are hardly trusted, but that in practice a physician is summoned at the same time" ⁹

⁹ Also see citation of B Stryk, *de jur scns diss*, in footnote 5

CASE REPORTS

AMYLOIDOSIS IN CHRONIC ATROPHIC ARTHRITIS*

By WALTER M. SOLOMON, M D , *Cleveland, Ohio*

SINCE amyloid infiltration was first brought to the attention of the medical profession by Rokitsky and the Viennese school only a few cases of amyloidosis associated with chronic arthritis have been reported. This relative sparsity of reports prompts the discussion of the following case.

Amyloidosis most frequently complicates tuberculosis and other diseases in which chronic suppuration occurs, such as osteomyelitis, pulmonary abscess, pyelonephritis and others. Certain chronic diseases which lack obvious suppurative processes but have occasionally shown amyloid deposits are Hodgkin's disease, cirrhosis of the liver, leukemia and myeloma. Amyloidosis has been found also in nonsuppurative infectious diseases such as syphilis, malaria, lymphogranuloma and chronic atrophic arthritis.

A few reports have appeared in the more recent literature of the presence of amyloidosis in association with chronic arthritis. Schneiderbauer,¹ Hardgrove² and Reimann and Eklund³ cite cases of typical atrophic arthritis, Moschowitz⁴ had two cases, one with atrophic arthritis and another which would be classified as infectious arthritis. Lengh⁵ reported one case of septic polyarthritis in which a renal infection was thought to have been the cause of the amyloid disease. Imrie and Aitkenhead⁶ had one patient and Portis⁷ had two patients who developed amyloidosis in the course of Still's disease (chronic atrophic arthritis of children). The patient of Koletsky and Stecher⁸ presented symptoms of chronic arthritis over a period of 14 years and at autopsy there was extensive amyloid involvement of the joints, bones and other structures. They classified this case as primary systemic amyloidosis. The patients reported by Feller,⁹ Michelson¹⁰ and Peila and Gross¹¹ are cases of primary amyloidosis in which arthritis was present. In these cases the amyloid was probably primary and in no sense a complication of the arthritis.

The importance of amyloidosis in chronic atrophic arthritis concerns its etiology. Many theories have been proposed for the presence of amyloid infiltration, but those factors which might be considered in the discussion of atrophic arthritis are the disease itself and the therapeutic use of parenteral injections. Without any attempt to review the already voluminous literature on the subject of amyloidosis the following case is reported.

CASE REPORT

L. P., a white male, was first seen in the dispensary of St. Alex Hospital at the age of 36 years. He had no other illness except arthritis, which began when he was 30 years old and followed the clinical course of the more severe and rapidly disabling

* Received for publication January 30, 1941.

From the Department of Medicine of the St. Alex Hospital and the School of Medicine of Western Reserve University.

form of chronic atrophic arthritis. When first seen the arthritic process had involved all the joints of the body. The vertebral column was immobile, with the neck fixed in 15° of flexion. There was severe deformity of both hands and wrists, and the fingers were ankylosed in approximately 45° of flexion. There was induration about the elbows and limitation of motion. Both shoulders had only limited impairment of motion. The knees were enlarged and could not be extended completely. The toes were deformed, and there was bilateral hallux valgus. The temporomandibular joints were partially ankylosed. No joint was acutely inflamed. The patient, though handicapped with his deformities, had been about after a fashion with the aid of two canes. The clinical symptoms and signs did not change materially during the three years of his visits to the dispensary until just before his death.

Injections of Crowe's vaccine subcutaneously were started soon after his first visit. Crowe's vaccine is a stock vaccine made in Dr H. Warren Crowe's Laboratory, London, and includes several strains of streptococcus and staphylococcus. These injections were given weekly during his three years' attendance at the dispensary and totaled 136. The amount of this mixed vaccine administered varied from 1000 to 15 000 organisms per week. For the first 26 weeks in addition to the Crowe's vaccine he received a weekly intravenous injection of colloidal sulfur 30 milligrams each or a total of 780 milligrams. The sulfur injections were discontinued but he continued to receive the Crowe's vaccine until one week before his death. He received no drugs or any other therapy during these three years. Though his diet was not ideal, it was not obviously deficient.

Eight months prior to his death, he was admitted to the hospital for further study. The pertinent findings at this time were: the heart showed a questionable systolic murmur at the apex; there was marked atrophic arthritic involvement of every joint; the urine had a specific gravity of 1.017, albumin two plus, microscopic, many fine and coarse granular casts, red blood cell count 4 400,000, hemoglobin 13 grams (white blood cell count 9550, sedimentation rate 122 mm in one hour (modified Westergren method), and the liver function test with iso-iodakon showed 5 per cent in 30 minutes and "too low to read" in one hour.

Shortly before his death he was readmitted to the hospital because of persistent vomiting and pain in the abdomen. At this time the examination disclosed heart, systolic and diastolic murmur at the apex, blood pressure 146 mm Hg systolic and 80 mm diastolic, the abdomen was rigid in upper half, and there was dullness on percussion. Laboratory findings—urine, specific gravity 1.011, albumin four plus, microscopic, many red cells, red blood cell count 3 200,000, hemoglobin 12.5 grams, white blood cell count 10,000, sedimentation rate 117 mm in one hour, blood urea nitrogen 180 mg, uric acid 9 mg, creatinine 6 mg. Soon after admission he lapsed into coma and died on the fourth day.

Autopsy Findings. Autopsy was performed by Dr John L. Work four hours after death. The body was that of a severely deformed, moderately emaciated asthenic white man appearing 5 to 10 years older than the stated age of 39 years. The deformities were those of chronic atrophic arthritis and were present in all the joints. The skin over the affected joints was tense, thin and shiny. There were shallow decubiti in the sacral region and the skin and mucous membranes were pale. There was moderate edema of both lower extremities and the scrotum. The mouth was edentulous. More fat was present in the subcutaneous tissues than was expected from the external appearance of the body. It was pale lemon yellow and had the normal consistency.

The heart weighed 375 gm. Except for nodular thickening and calcification at the base of the anterior mitral leaflet there was nothing noteworthy. The lungs were the seat of apical scars and severe edema and there was bronchopneumonia on the right side. No primary tuberculous foci were demonstrated. The liver

weighed 1975 gm. Its edges were blunt and its capsule was tense. The parenchyma was firm but friable. The cut surfaces bulged slightly and were dull reddish brown, shiny and translucent. The markings were hazy. There was cholesterolemia of the gall-bladder. The spleen weighed 140 gm. The cut surfaces were flat, reddish gray, and yielded very little blood or pulp when scraped. The adrenal glands showed no gross abnormalities. The right and left kidneys weighed 150 and 125 gm. respectively. The parenchyma of both was firm and peculiar, dull pinkish gray. The de-capsulated surfaces were dotted with rosettes of tiny dilated blood vessels and punctate hemorrhages. There was slight bulging of the cut surfaces. There was a reduction in the thickness of both cortex and medulla and the ratio of the one to the other was reduced. The markings were indistinct or completely obscured and the cortices were studded with pearly gray dots. The pelvis and calices were normal. There was no deformity of the thoracic or lumbar segments of the spine, but sections through the vertebral bodies showed abnormally thin cortices and delicate trabeculae. The bone marrow was pale pink and pulsatous.

Microscopic preparations revealed marked amyloidosis of the liver, spleen and both kidneys. The degree of involvement in the liver and spleen was much greater than their gross appearance indicated. In the liver the amyloid was present in the usual situation. In the spleen it was confined to the follicles. Sections through the kidneys showed lobulated collections of amyloid between the epithelium and the capillary endothelium of all glomerular tufts. The tufts were enlarged, bloodless and frequently fused with their capsules. The capsular epithelium was swollen and there was mild sub-capsular fibrosis. There was a reduction in the number of tubules and those which remained were dilated. There was diffuse fibrosis of the interstitial tissue and an infiltration of fibroblasts, lymphocytes, large mononuclear cells and varying numbers of eosinophiles and plasma cells. The arteries and arterioles showed no significant abnormalities. Small amounts of amyloid were present in the cortex of both adrenal glands.

The anatomical diagnosis was, chronic atrophic arthritis, amyloidosis of the kidneys, liver, spleen and adrenal glands, edema of the lungs, marked, and bronchopneumonia.

COMMENT

The patient is a typical case of atrophic arthritis. The disease was sufficiently severe to cripple him in relatively few years. The disease was definitely chronic with clinical and laboratory evidence of a low grade infectious process. There was no suppuration either grossly or microscopically. Thus none of the conditions ordinarily associated with the deposition of amyloid were present in this case, yet in distribution and character it was characteristic of secondary amyloidosis. The tuberculosis in the apices of both lungs was slight and anatomically healed, and the changes in the kidneys appeared to be the result rather than the cause of the amyloid. Consequently, from a combined clinical and anatomical standpoint the likely causes of the amyloidosis are the chronic atrophic arthritis itself, the vaccine therapy, or a combination of the two. If chronic atrophic arthritis alone causes amyloidosis, it is difficult to explain the fact that so few cases have been reported. It is doubtless true that comparatively few patients with atrophic arthritis die in those hospitals in which autopsy permission is actively sought. During the past 24 years there were only six autopsies in a total of 15,000 available autopsy records in which a diagnosis of chronic atrophic arthritis was made, and in none of these was there amyloid in any structures. Certainly the autopsy records of the average hospital, in this city at least, fail to

indicate the true incidence of chronic atrophic arthritis in the general population. However, even though so few cases are seen at autopsy, it would seem that if amyloidosis were present more frequently in this relatively common disease, it could be confirmed by the adequate clinical signs and laboratory tests which are now available.

The factor of vaccine therapy should be considered. For a period of three years the patient received weekly parenteral injections regularly and frequently, missing only 17 injections in a total of 168 weeks. The vaccine used was made from streptococcic strains, which are thought to be more potent factors in the production of amyloid.

Reimann and Eklund⁸ reported a case of a patient with chronic atrophic arthritis who received 41 injections of a streptococcus vaccine intramuscularly and intravenously over a period of 22 months. They came to the conclusion that "because of the rarity of the occurrence of amyloid disease in chronic arthritis and the frequency with which it occurs following long continued parenteral injections of numerous substances including vaccine, it was believed that vaccine therapy was responsible for amyloidosis in this case."

Dick and Leiter¹² produced amyloidosis in rabbits within eight months by the use of 17 bacterial strains which included hemolytic and green strains of streptococcus and Friedlander's bacillus. They found that the freshness of the bacterial strain seemed to be more important than the dosage in determining the rate and degree of amyloid production. Two observers^{13, 14} noted that between 60 per cent and 80 per cent of horses used for the production of antisera developed amyloidosis. It was interesting to note that the horses employed for the production of scarlet fever antisera showed a greater incidence of amyloidosis than those used for diphtheria and tetanus antitoxin. Hardgrove² rapidly produced amyloid in mice by the injection of *Bacillus coli* and staphylococci and various proteins. However, bacterial vaccines and toxins are not the only substances which are known to cause amyloid disease. Lettieri¹⁵ produced it by repeated injections of casein, peptone, egg albumin, cereal albumin, gelatin, nuclein and implants of normal spleen and kidneys. Grayzel and his colleagues¹⁶ maintain that in order to produce amyloidosis with these products the whole protein compound must be used, for if intermediary or split products are used amyloidosis will not occur. In a Cabot Case Record report¹⁷ the subject a case of atrophic arthritis with amyloidosis, had received injections of amidoxal benzoate during a period of nine months. Eklund and Reimann¹⁸ also reported from the literature that the parenteral use of such substances as silicates, manganese chloride, sulfur, selenium, turpentine and others was followed by amyloidosis.

Two other patients from the dispensary received the Crowe vaccine by injections for approximately the same length of time and as regularly as the case which is reported without evidence of amyloidosis.

Dr H. Warren Crowe has personally used his vaccine extensively for many years at his clinic in London and the same vaccine has been employed in many clinics throughout the world. Also other types of vaccines which are widely used in other clinics in the treatment of atrophic arthritis include intravascular strains of streptococci. Thus it would appear that if parenteral injections of vaccines, particularly of streptococci, are possible agents for the production of amyloidosis the complication would occur frequently. However, it is not clear

been reported in human cases. Furthermore, in tuberculosis, the disease with which amyloidosis is most frequently seen, parenteral therapy is seldom employed. It is, therefore, difficult to consider parenteral injections per se as the most important etiological factor for human amyloidosis.

SUMMARY

A case of atrophic arthritis is reported with amyloidosis of the spleen, liver, kidneys and adrenals. Whether the amyloidosis in this case of arthritis was a complication of the disease, a result of the repeated injection of a vaccine containing strains of streptococci, or the combined effect of the two cannot be positively stated.

BIBLIOGRAPHY

- 1 SCHNEIDERBAUER, A. Amyloid and lipid nephrosis in chronic polyarthritis, *Ztschr f klin Med*, 1938, **CLXXXIII**, 643-647
- 2 HARDGROVE, MAURICE A. F. Retention of Congo red in amyloid disease, *Arch Path*, 1933, **11**, 238-243
- 3 REIMANN, HOBART A., and EKLUND, CARL M. Long continued vaccine therapy as a cause of amyloidosis, *Am Jr Med Sci*, 1935, **CLX**, 88
- 4 MOSCHCOWITZ, E. Clinical aspects of amyloidosis, *ANN INT MED*, 1936, **1**, 73-78
- 5 LENGH, F. Case of amyloid deposits in joints, *Zentralbl f allg Path u path Anat*, 1937, **LXIV**, 1-5
- ✓ 6 IMRIE, A. H., and AITKENHEAD, A. C. Amyloidosis complicating Still's disease, *Lancet*, 1939, **II**, 421
- ✧ 7 PORTIS, ROBERT B. Pathology of chronic arthritis of children (Still's disease), *Am Jr Dis Child*, 1938, **IV**, 1000-1017
- ✓ 8 KOLETSKY, SIMON, and STECHER, R. M. Primary systemic amyloidosis, *Arch Path*, 1939, **LXVII**, 267-288
- 9 FELLER, F. Case of amyloid, *Zentralbl f allg Path u path Anat*, 1935, **LXIII**, 123
- 10 MICHELSON, H. E., and LYNCH, F. W. Systematized amyloidosis of skin and muscles, *Arch Dermat and Syph*, 1935, **XXXII**, 363-369
- 11 PERLA, DAVID, and GROSS, HARRY. Atypical amyloid disease, *Am Jr Path*, 1935, **11**, 93-112
- 12 DICK, G. F., and LEITER, L. Amyloidosis and hyperglobulinemia, *Trans Assoc Am Phys*, 1937, **LI**, 246-249
- 13 ARNDT, H. J., and DOERKEN, E. Amyloidosis in horses used in preparations of serums, *Arch f wissensch u prakt Tierh*, 1931, **LXIII**, 1-11
- 14 SIPOS, J. Abstr in *Hajrest Veter Med*, 1930, **1**, 795
- 15 LETTERER, E. Studies concerning the formation of amyloid, *Beitr z path Anat u z allg Path*, 1926, **LXXV**, 486-588
- 16 GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., and BOLKER, H. Amyloidosis, *Arch Path*, 1933, **XVII**, 50-75
- 17 Cabot Case Record—Case 19142, Chronic arthritis with recent edema of the feet, *New England Jr Med*, 1933, **CCVIII**, 757-759
- 18 EKLUND, C. M., and REIMANN, H. A. The etiology of amyloid disease, *Arch Path*, 1936, **XXI**, 1-9

CHRONIC COR PULMONALE WITH REPORT OF A CASE

By GEORGE W. COVY, F A C P, *Lincoln, Nebraska*

LESIONS affecting the lesser circulation occur less frequently than those of the systemic. There is less chance of direct observation of these lesions, and the diagnosis of the conditions must be made by less direct methods than is the case where one is dealing with the commoner cardiovascular diseases.

It is customary to speak of right or left heart failure but such statements require a certain amount of mental reservation because of the closely integrated and interdependent functions of the lesser and greater circulations. Any degree of failure of either one immediately jeopardizes the anatomical and functional integrity of the other and reduces the chance of properly supplying oxygen to the organs and tissues of the body.

As Dry¹ has pointed out, any consideration of the diseases affecting the flow of blood through the pulmonary area must recognize that here, as in other organs, a great vascular reserve is provided, there being a "vascular area and a capillary bed far greater than ordinary functional demands can exceed."

The systolic blood pressure in the pulmonary artery of man is normally low, being about 20 mm of mercury. The comparatively delicate structure of the pulmonary arterial tree and the thin wall of the right ventricle are anatomical evidence of this low normal pressure.

Obstruction to the flow of blood through the pulmonary circulation leads to increased pressure within this system. This rise in pressure, if maintained over a period of time, leads to sclerotic changes in the pulmonary arteries and arterioles and to hypertrophy of the right ventricle.

In this connection it has been shown by Haggart and Walker² that slightly more than half the pulmonary vascular bed can be obstructed without seriously affecting the circulation in general. If this amount is exceeded even slightly, circulatory failure is precipitated. Whether this holds true when the obstruction takes place slowly and progressively does not appear to have been answered. The experiments on which these figures are based made use of acute obstruction only.

Waring and Black³ show, diagrammatically, the various points in the pulmonary circulation at which obstruction may take place from congenital heart disease with arteriovenous shunt, on one hand, to mitral stenosis on the other and including pulmonary valve, pulmonary artery or its larger branches, pulmonary arterioles, the capillary bed, the veins and finally the mitral valve.

Obstruction at the mitral valve is doubtless the most common point but its location beyond the capillary bed produces little effect on oxygenation until circulatory failure supervenes, consequently the picture, when recognized, is imprecise and complicated.

Obstruction due to disease of the pulmonary veins is very uncommon. That due to obliteration of the capillary bed must be very extensive in order to produce "cor pulmonale" because here lies the greatest vascular reserve. Such conditions as diffuse carcinomatosis of the lungs, extensive pulmonary fibrosis, etc., are some of the causes which may produce typical symptoms by obstruction in this area. The question of emphysema per se as a cause of obstructive

* Received for publication December 31, 1940

tion in the capillary bed to produce increased blood pressure and right ventricular hypertrophy seems to be one on which opinion differs

Probably conditions affecting the vascular bed of the lungs on the arterial and arteriolar side furnish the purest examples of overload and failure of the lesser circulation. Massive emboli occluding the main stem of the pulmonary artery or largely occluding both main branches are usually promptly fatal, through shock and anoxemia. These constitute a large percentage of the cases observed. Slower occlusion at this same point by a somewhat similar mechanism is uncommon. Baines and Yater⁴ report a case of failure due to an old thrombus in the main trunk and both branches of the pulmonary artery probably arising some three years before death, as emboli from an infected hand. Somewhat similar cases have been reported by Means and Malloy,⁵ and by Jump and Baumann.⁶ It is a case of this type which I wish to report.

CASE REPORT

H. I. McV was first observed in 1934, complaining chiefly of thrombophlebitis in the left leg. There had been thrombophlebitis in the right leg in 1931. The original attack was preceded by "influenza" and accompanied by chills and fever. The present attack was preceded for two or three days by pain in the abdomen and distention with gas. There had been three or four attacks of abdominal pain of similar character accompanied by palpitation since 1931. Questioning brought out the facts that he was troubled by a dry non-productive cough and by dyspnea on exertion.

The only other history of possible importance was of an operation for varicocele on the left, in 1917, and the fact that he smoked about 30 cigars a day while engaged largely in indoor work.

Physical examination revealed, in addition to the signs of old and recent thrombophlebitis: temperature, 99.4° F, pulse, 104, blood pressure, 134 mm Hg systolic and 68 mm diastolic, atrophy of the left testicle, slight right varicocele and dilated veins on the surface of the scrotum. The lung fields were clear, and the heart was apparently normal save for tachycardia. The remainder of the examination was negative. No further investigation of the cardiovascular system was made at the time. The tachycardia, cough and dyspnea were blamed upon the acute process and the heavy smoking.

His urine was acid, the specific gravity was 1.032, and several red cells were seen per high power field in the centrifuged specimen. Several hyaline casts were seen. The hemoglobin was 16.4 grams per 100 c.c. and erythrocytes 4.08 millions. White and differential counts were not remarkable and the blood Wassermann reaction was negative.

Under the usual treatment the condition of the leg improved, the blood cells disappeared from the urine and, coincidentally, the dyspnea and cough were relieved.

Four years later the patient was seen again because for six months he had felt exhausted and weak and, on exercise, there were dyspnea, palpitation and weakness in the legs.

Physical examination revealed temperature, 98.4°, pulse, 90, blood pressure, 124 mm Hg systolic and 80 mm diastolic. He appeared somewhat pale. The arteries in the neck pulsated more than normally. There was no dependent edema, no swelling of the liver, and no râles at the lung bases. The percussion note over the lungs was booming and the breath sounds feeble suggesting emphysema. He was not cyanotic. He had always had prominent eyes and this feature seemed somewhat exaggerated. There was a tremor of the hands.

The urine was normal. The hemoglobin was 18 grams per 100 c.c., red cells numbered 4.42 millions. Basal metabolic rate determinations were minus 19, plus

8 and minus 5 per cent over a period of two months, during which time he received small doses of thyroid extract

The full significance of the symptoms was not appreciated at this time, but the patient was required to rest a great deal and soon he was symptomatically greatly improved. The symptom which never left him was dyspnea on exertion.

He returned in six months because, on resuming his usual activities, all the symptoms came back and were exaggerated. Exertion tended to bring on paroxysms of severe cough. These also occurred at night and, on at least two occasions, he lost consciousness momentarily during the coughing. Cyanosis now accompanied the dyspnea after exertion or on severe coughing.

At this time the pulse was 96 and blood pressure 120 mm Hg systolic and 90 mm diastolic. There was no dependent edema, no enlargement of the liver, nor râles in the lungs.

Fluoroscopic examination of the chest revealed a large heart with thickened vascular markings in the hila but no unusual pulsation was noted in the hilar vessels. Films at 72 inches (figure 1a) showed the heart to be enlarged to 52 per cent of the diameter of the chest. Enlargement was both to right and left and the shadow was of a globular shape. There was a marked bulge in the region of the pulmonary artery.

The electrocardiogram (figure 1b) showed a slight tachycardia and a marked right ventricular preponderance, with no other distinctive abnormalities.

The urine contained a strong trace of albumin and an occasional erythrocyte. The hemoglobin was 116 gm per 100 cc, and red cell count, 4.74 millions per cu mm.

It was now recognized that we were dealing with a chronic cor pulmonale with signs of circulatory failure. These signs and symptoms were as follows: gradually increasing dyspnea out of all proportion to any other evidence of congestive heart failure. In particular, there had been no râles at the pulmonary bases. The dyspnea had been accompanied by an increasing degree of cyanosis on strain, such as cough or exertion. Accentuation of the pulmonary second sound, which is so often mentioned, was not a marked feature in this case. The roentgen examination revealed the typical right heart enlargement with prominence at the pulmonary cone. The electrocardiogram was characteristic with its evidence of marked right ventricular preponderance. That this picture was not due to mitral stenosis was obvious because of the absence of significant murmurs and of left auricular enlargement as proved by the roentgen observations.

Hospitalization with rest and digitalis caused marked improvement which lasted only until an attempt was made to permit physical activity. Then all the symptoms recurred and in addition, there were dependent edema, enlargement of the liver and finally, ascites. Râles were never heard in the lungs until the final week of life. Hemoptysis did not occur. Dyspnea remained the leading symptom. Cyanosis became more marked as a terminal feature but not to the extent suggestive of the so-called "black cardiac." He was, consequently, kept at rest much of the time.

Early in 1939 the patient was examined by Dr. T. J. Dry at the Mayo Clinic. An instructive additional finding was reported by him. This was an increase in circulation time from the normal 14 seconds to 35 seconds—arm to tongue as determined by injection of 5 cc of decholin. It was assumed that the slowing was in the pulmonary circuit.

On two occasions when compensation was at its best a faint continuous murmur with systolic accentuation was heard over the pulmonary area.

The patient was comfortable at almost complete rest and with digitalis administration until July, 1939 when dyspnea increased, orthopnea became marked, cyanosis on, and increased, and edema, liver enlargement and ascites became more pronounced. Venous pressure was markedly increased. On lying down the veins of the head and neck became tremendously distended and cyanosis of the lips became marked.

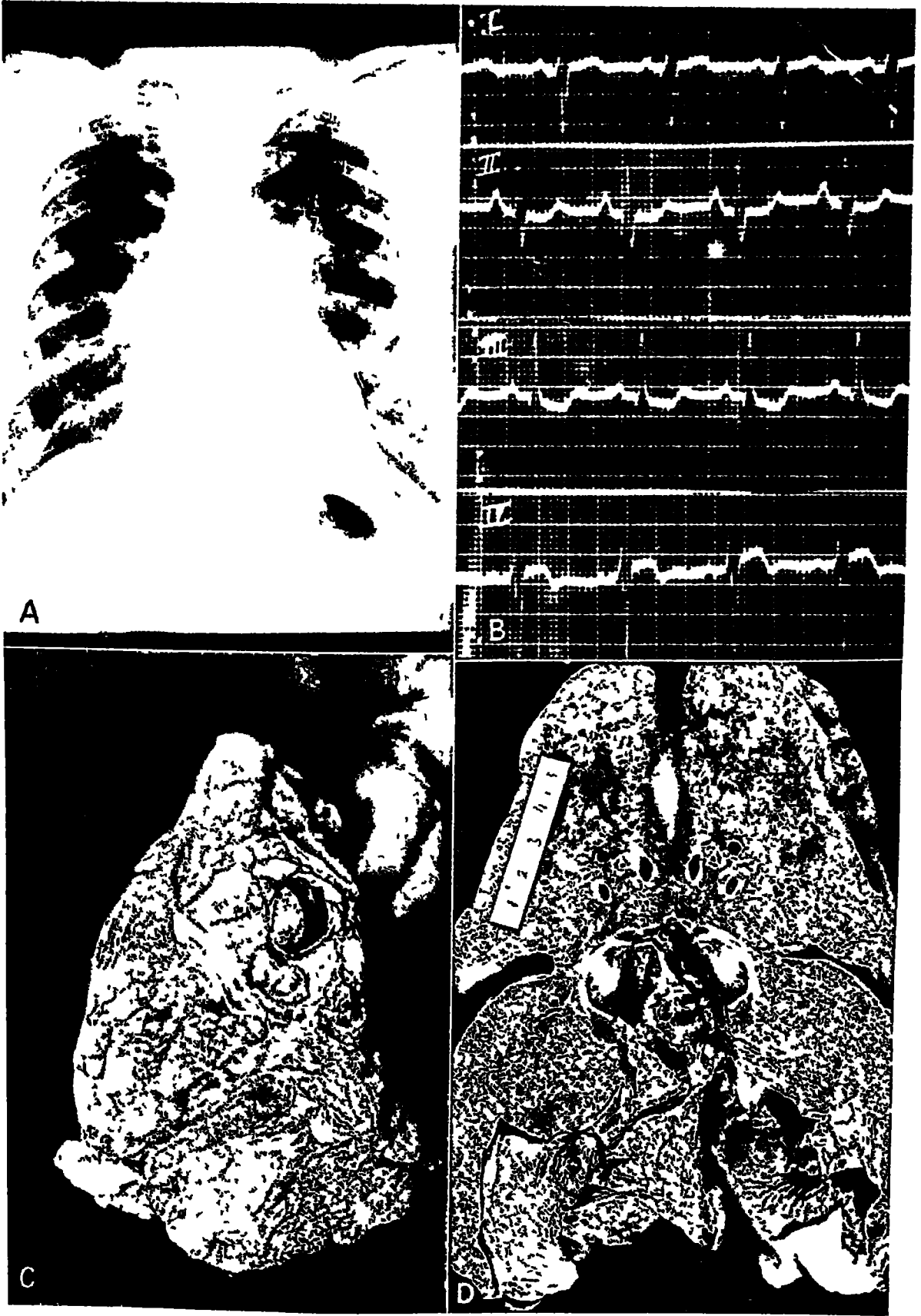


FIG 1

In the last few hours oxygen was given and no quantity up to 7 liters per minute made the slightest difference in his dyspnea and cyanosis. The heart became slower and the rhythm was broken by frequent ectopic beats. Gallop rhythm became so marked it seemed as if the ventricles were alternating in their contractions. A systolic murmur was audible over each valve area. The pulse was feeble and the blood pressure fell rapidly.

The clinical diagnosis at death on September 23, 1939 was chronic cor pulmonale due to some obstructive lesion in the lesser circulation, probably arteriolosclerosis.

At autopsy the important findings were confined to the heart and lungs. The heart was both dilated and hypertrophied, the weight being 560 grams. Its transverse diameter was 16 cm. The dilatation involved all chambers and was accompanied by relative insufficiency of mitral (10 cm), tricuspid (15 cm), and pulmonary (10 cm) valves. The hypertrophy involved the right ventricle largely, its wall having a maximum thickness of 1 cm. The wall of the left ventricle was not thickened, the aortic valve and aorta throughout its length were normal.

The anterior surface of the heart was composed largely of right ventricle, the apex being very blunt and composed of right ventricle. The left ventricle could be seen at the obtuse margin. The right atrium was greatly dilated and its wall was somewhat fibrous in appearance. The pulmonary cone was greatly dilated. The coronary arteries were normal.

In each main pulmonary artery, beginning at about its middle, there was a large firm thrombus. This was securely attached in each instance to the anterior aspect of the artery wall (figure 1c). The maximum thickness of the thrombus was 1.5 cm. The lumina were so nearly filled by the thrombus that only a small crescent-shaped opening remained. This was filled with recent clot which may have been post mortem.

These old thrombi extended into the secondary branches of the artery, in some instances completely filling vessels of 1 cm or more in size (figures 1d and 2a and 5b). The cut surfaces of the thrombi showed differences in color and consistency suggesting accretion over a period of time but did not appear to have become organized in any portion.

The right lung showed three dimpled scars in the pleura over the lower lobe. Beneath each of these was an area of fibrous tissue. There was also a recent infarct 2 cm in diameter at the pleura. Near the lower margin of the left lung was a similar small recent infarct.

The large and medium sized branches of the pulmonary artery show a moderate streaking with atherosclerosis. The peripheral pulmonary tissue showed an obvious vesicular emphysema.

In addition to these findings there were ascites, bilateral slight pleural effusion, moderate pericardial effusion, pleural and pleuropericardial adhesions on the right, chronic passive congestion of the liver and spleen and an old healed infarct of the right kidney.

Microscopic examination of the old thrombus showed that the portion near the intima had undergone organization whereas the more peripheral portions were largely fibrin in various stages of hyalinization. The outer layer of the artery wall where the old thrombus was attached showed extensive perivascular lymphoid cell infiltration.

The smaller arteries showed thickened medial coats with corresponding reduction of the lumina. Many were occluded by organized thrombi. In many instances small

FIG 1 (a) Roentgenogram showing enlarged heart, prominent pulmonary cone and thickening of the hilar shadows. Note that the cardiac enlargement is marked toward the right and relatively less toward the left. (b) Electrocardiogram of this patient showing principally right ventricular preponderance. (c) Medial surface of lung. Note the large pulmonary artery containing an old thrombus with a crescent-shaped patent portion lining the patent portion of the lumen. (d) Section deeper in the lung showing complete occlusion of the pulmonary artery by old thrombus.

ization of these thrombi had taken place (figure 2b) The arterioles, as a rule, showed no change

There were areas of atelectasis and larger areas of emphysema Many heart failure cells were scattered throughout the lung

The sections of heart showed little beyond a marked hypertrophy of the individual fibers of the right ventricle which contrasted sharply with those of the left ventricle

Examination of the remainder of the organs showed nothing but the expected changes

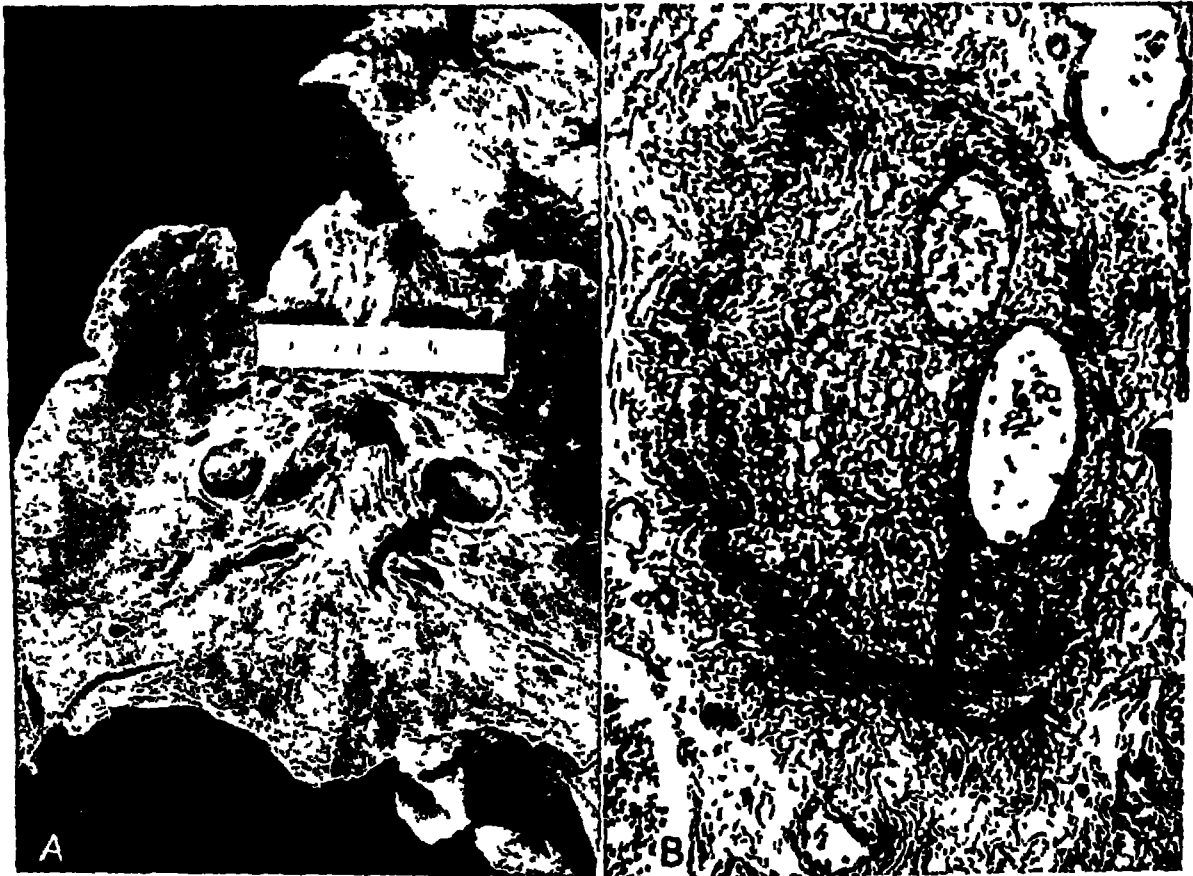


FIG 2 (a) A section deeper into the lower lobe showing complete occlusion of branch of pulmonary artery 1.3 cm in diameter (b) Microscopic section showing small artery which has been completely thrombosed and recanalized

DISCUSSION

The leading symptom in this individual was dyspnea It was disproportional to the signs of congestive heart failure There was but slight polycythemic response, and cyanosis occurred late Right ventricular hypertrophy was obvious in the roentgenograms, and right ventricular strain was reflected by the electrocardiogram There were no signs of pulmonary congestion until very late, when the left heart began to fail probably as a result of chronic anoxemia

The life history of the lesion in the pulmonary arteries is not clear Two episodes of thrombophlebitis, the first eight years before death and the second years before death, suggest the possibility of embolism followed by gradual organization of the thrombus, yet no definite history suggesting such embolic epi-

sodes could be obtained either from the patient or his wife. There is a possibility that the pulmonary artery participated in a primary vascular inflammatory process giving rise to mural thrombosis and that these thrombi grew by accretion until the clinical picture, as seen years later, gradually developed. There is some evidence to support the latter contention, inasmuch as the wall of the pulmonary artery showed some cellular infiltration suggestive of old inflammation and the clot was laminated, the oldest part lying next to the artery wall.

The amount of arteriolar sclerotic change was minimal and can be left out of consideration as a factor in producing anoxemia.

A certain amount of sclerotic change was present in the main stem and larger branches of the pulmonary artery but was inconsequential in amount when considered in relation to the symptoms. It was the effect, not the cause of increased intrapulmonary blood pressure.

SUMMARY

1 The physiologic and pathologic consequences of obstruction in the pulmonary vascular bed are briefly reviewed.

2 A case of old bilateral thrombosis of both primary branches of the pulmonary artery is reported. This patient had the cardinal symptoms and signs of chronic cor pulmonale. This diagnosis was possible ante mortem, though the exact nature of the pathologic factor responsible for the clinical syndrome in this case could not be determined until autopsy.

BIBLIOGRAPHY

- 1 DRY, THOMAS J. Problems associated with the clinical recognition of pulmonary hypertension, *Minnesota Med*, 1938, **31**, 535.
- 2 HAGGART, G. E., and WALKER, A. M. The physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery, *Arch Surg*, 1923, **77**, 764.
- 3 WARING, JAMES J., and BLACK, W. C. The syndrome of obstruction of the lesser circulation, *Am Jr Med Sci*, 1934, **138**, 652.
- 4 BARRETS, ARTHUR R., and YATTE, WALLACE M. Failure of the right ventricle due to an ancient thrombus in the pulmonary arteries, *Med Clin N Am*, 1929, **3**, 1610.
- 5 MEANS, J. H., and MALLORY, T. B. Total occlusion of the right branch of the pulmonary artery by an organized thrombus, *ANN INT MED*, 1931, **1**, 417.
- 6 JUMP, H. D., and BALMANN, FRIDT. Large thrombus of the pulmonary artery with chronic cyanosis and polycythemia, *Pennsylvania Med Jr*, 1929, **33**, 754.

CALCIFICATION OF LEFT VENTRICULAR INFARCTION RECOGNIZED DURING LIFE*

By MILTON C. BORMAN, M.D., F.A.C.P., *Midwestern University*

CALCIFIED myocardial infarcts have been rarely found during life, and still more rarely proved at necropsy. Calcification in the heart was diagnosed during life by roentgen-ray in 1911 by F. M. Groedel.¹ The first case thus recognized and proved by necropsy was that of Thomas Scholtz in 1927.² Croft and

* Received for publication October 21, 1940.

From the Medical Service, Sacred Heart Hospital, Milwaukee, Wisconsin.

Levine³ in 1937 reported the second case, which was also studied with the electrocardiograph. Parkinson⁴ in 1938 added a third case proved at necropsy. Ours, the fourth case, was first discovered by roentgen-ray, and was studied with heart tracings and the kymograph. White⁵ has stated that in rare cases actual bone is found in the myocardium instead of mere masses of lime salts. Necropsy in our case showed histological evidence of true bone formation. We have found seven other instances in the literature in which the calcium apparently has been absorbed and redeposited with the formation of true bone.

CASE REPORT

A white male, 74 years old, entered the Sanitarium complaining of cough. There had been moderate dyspnea for one year. Three months previously he had a temperature of 103° F, with paroxysms of coughing productive of thick pyoid material. He was tired, could not get his strength back, had insomnia and nycturia. The remainder of his history was negative with the following exception. Nineteen years previously while caring for his furnace after breakfast he had had a momentary attack of sharp sticking substernal and epigastric pain, which took his breath away. After lunch, while selling bonds, he had a second similar but more severe attack which lasted an hour or two. Thirty-five minutes after his evening meal he had another attack. A physician was called at 10:30 p.m., made a diagnosis of angina pectoris, and gave him more than one hypodermic of morphine sulphate before leaving the bedside. He remained in bed 18 days, up about the house for 12 days, and then returned to light work schedule for eight months before resuming his regular work.

He was of sthenic habitus, 66" tall, weighing 181 pounds. There were a few transient râles at both lung bases. The liver edge was not palpable. Blood pressure was 168 mm Hg systolic and 100 mm diastolic. Heart sounds were subnormal in

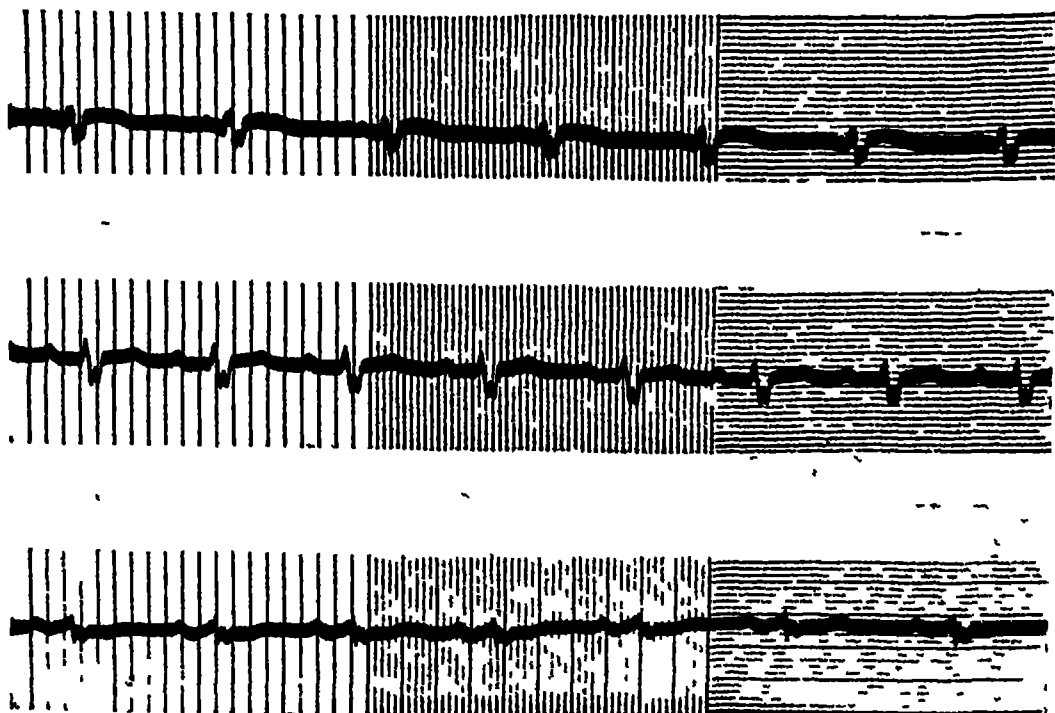


FIG 1 Tracing 2 years before death showing low voltage, p-r 0.24 sec. Small Q, slurred R complexes (0.15 sec). RT, elevated 1.3 mm. RT₂, elevated 0.5 mm. RT₃, depressed 0.3 mm. T₁, isoelectric, T₁₋₃, slightly positive. T₁, or anterior type infarction, topographically, or the superficial sino-spiral muscle using Robb and Robb specific localization.

intensity, without murmurs, the apex not visible or palpable, and there was a gallop rhythm due to reduplication of the first sound

Clinical impression Organic heart disease (arteriosclerosis-hypertension, coronary disease, gallop rhythm, Class 2b)

Laboratory findings Complete blood count negative Urinalysis showed a trace of albumin and an occasional hyaline cast

Electrocardiographic study showed low voltage, p-r 0.24 second Small Q, slurred R₁₋₃, main deflections being negative in Leads I and II, and QRS 0.15 second duration RT₁ elevated 1.3 mm, R T₂ elevated 0.5 mm RT₃ depressed 0.3 mm T₁ or anterior type infarction, topographically, or the superficial sino-spiral muscle involvement using Robb and Robb specific localization (figure 1)

Roentgenographic studies and fluoroscopic examinations showed vascular pulmonary engorgement The heart was enlarged to the left, and the left portion of the



FIG 2 Posteroanterior teleroentgenogram Heart markedly enlarged to the left, large oval area of calcification superolaterally located in apex of the left ventricle measuring 9 by 6 cm. Small arrow in mid-left ventricle indicates calcification in proximal branches of the left coronary artery. Arrow near inferior margin indicates aortic calcification.

heart, including the apex and lower third of the left border, was occupied by a dense ringlike shadow, which formed an oblong ring. The vertical diameter of this ring was 10.5 cm, transverse diameter was 8 cm and 0.5 cm in thickness. This was well visualized by Bucky radiographs in a-p, p-a, and right oblique positions. It was definitely established that the deposit of calcium extended to the edge of the lower left portion of the heart. In the lateral position the shadow had the appearance of a quarter-moon. Measurements. T 32.0 cm, m-r 6.0 cm, m-l 12.5 cm, t-t 18.5 (57.812 per cent). The aorta was elongated, the knob prominent to the left. It was believed from these findings that the ringlike shadow was probably calcium deposit in an old infarct following coronary occlusion, and was in the parietal wall of the left ventricle (figure 2).



FIG 3 Posteroanterior kymogram. Almost complete absence of ventricle pulsations about midway between base and apex (Large arrow). Smaller arrow in lower frames shows almost complete absence of movement of calcified myocardium apex.

The patient rested six weeks in bed, began graduated exercises, and improved. His blood pressure fell to 126 mm Hg systolic and 76 mm diastolic. The gallop rhythm disappeared permanently on the ninth day, he lost 10 pounds, and returned home feeling much better.

About six months later kymograms showed a rather markedly diminished left ventricle contraction at the level of the nest-form calcification in the apex of the heart. The entire left ventricle was not involved in this diminished pulsation, the basal portion of the left border and the posterior border showing normal amplitude of excursion (figure 3).

Fourteen months later he returned with crepitant râles over the base of the left lung. Pulse rate was 96. Blood pressure was 150 mm Hg systolic and 82 mm diastolic. There was a tendency toward gallop rhythm, the tone quality of the heart sounds being poor. Heart tracings including Lead CF IV showed Q_1 more definite, and T_1 and T_2 slightly more positive. There was little if any depression in RT_1 . Absence of P_1 and a large Q_1 . RT_1 elevated (figure 4).

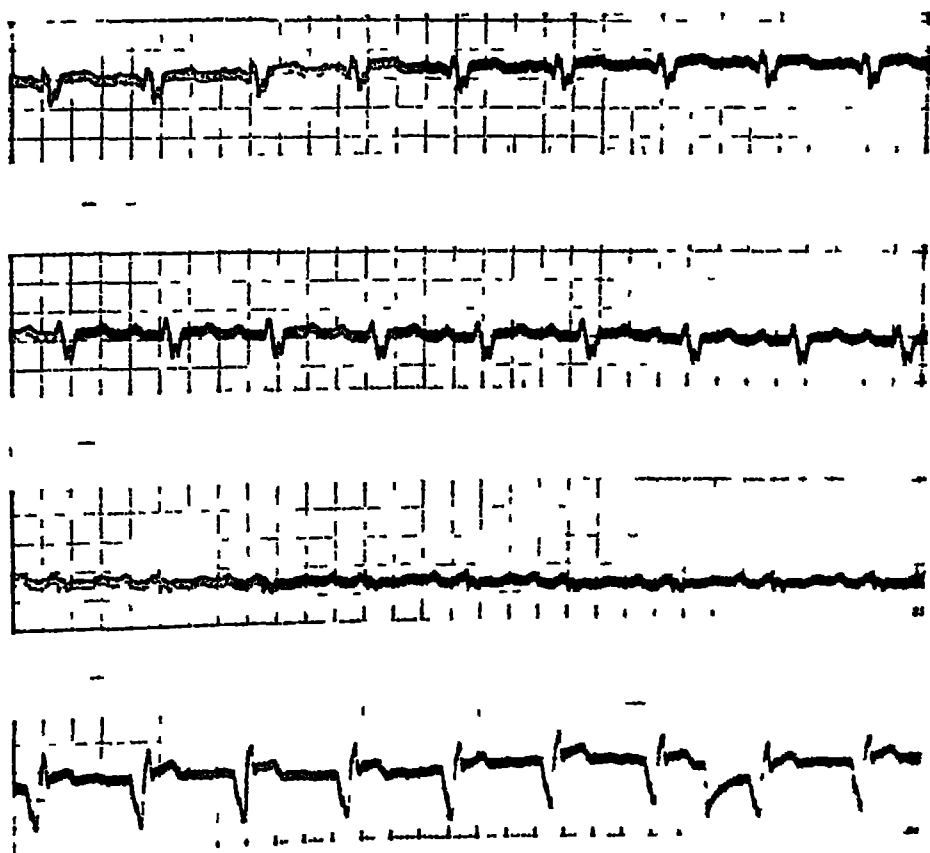


FIG. 4. Taken 9 weeks before death includes Lead CF IV. T_1 and T_2 slightly more positive. Little if any depression in RT_1 . Q_1 more definite. Lead IV shows absence of P wave and has a large Q_1 . RT_1 elevated and T_1 falls at the highest point of RT_1 at its termination.

Five weeks later he died in bed after climbing three flights of stairs to deliver a speech.

Postmortem examination. The only noteworthy finding was the calcification of the heart. It measured 16 cm from base to apex and 15 cm in width at the base.

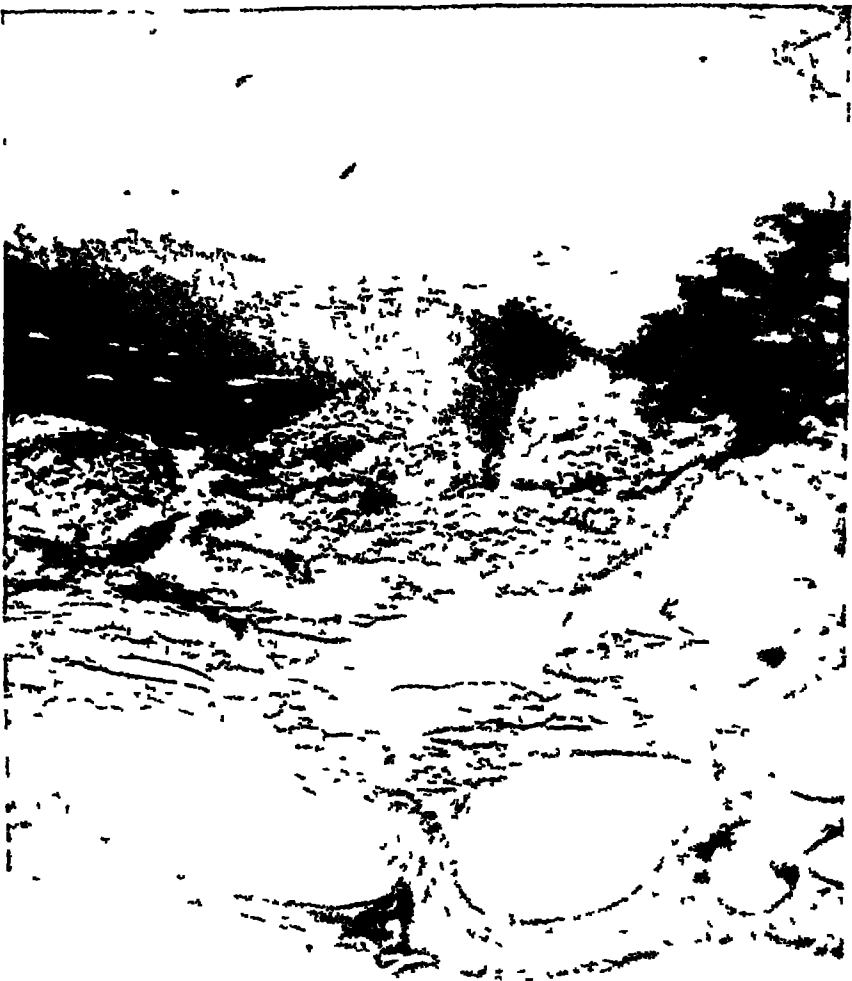
It weighed 725 grams. The pericardium was almost universally adherent, with moderate extrapericardial fat. The anterior surface of the left ventricle had a firmly rounded, bulging appearance involving the lower half of the left ventricle and apex and was about 10 cm in diameter, and separated from the upper portion of the left



FIG 5 Left ventricle exposed. The width of the heart muscle in the upper third of the left ventricular wall was 2.5 cm. Note the narrow wall and aneurysmal pouching of the lower two-thirds of the anterior left ventricular wall where the heart muscle has been replaced by scarring and calcification.

ventricle by a faintly visible and palpable groove. On palpation this bulging portion felt like bone and extended around the apex and along the posterior wall of the left ventricle for about 2 cm. Postmortem roentgenograms showed this calcification. When the left ventricle was opened (figure 5), it was seen that the area disclosed on the external aspect of the left ventricle corresponded to the wall of an aneurysmal

dilation, the wall of the aneurysm varying from 7 to 14 mm in thickness. Its cut surface was gray-white and firm. Embedded in the wall between the layers of scar tissue and remnants of myocardium were plaques of calcification, some of which seemed to be ossified. The lining of the aneurysm was covered by a laminated partially organized blood clot. At the apex there was a more recent partially organized polypoid mass of mural thrombus slightly more hemorrhagic and covered by fibrin. The aortic cusps were slightly sclerosed at the bases, and there were occasional streaks of fatty plaques on the intima of the aorta. The orifices of the coronary arteries were narrow. The main stems of both coronary arteries were greatly thickened and lined by atherosclerotic plaques, some of which were calcified. The anterior de-



scending branch of the left coronary was rigid and its lumen barely discernible. Other branches of the coronary arteries presented advanced calcification. Nowhere was there any gross evidence of recent thrombus formation.

Microscopic examination showed recanalization of old occlusions in the vessels, with intramural plaques of calcification frequently surrounded by remnants of scar tissue and myocardium in the wall of the aneurysm. In other areas definite bone formation could be demonstrated (figure 6).

The heart was preserved and presented to the Heart Museum of the University of Wisconsin Medical School, Madison, Wisconsin.

DISCUSSION

Although calcification of the pericardium is seen occasionally, calcified heart muscle has been reported uncommonly, and actual bone formation has been reported in seven instances. Calcification may follow metastatic deposit of calcium or toxic myocardial damage. About 9 per cent of the myocardial calcification reported has followed coronary sclerosis and thrombosis. The increasing incidence of coronary disease, our improved knowledge of diagnostic criteria, and our increased facilities for more complete study of cases of coronary disease, will, no doubt, lead to increased finding of myocardial calcification.

Scholz² says that like other pathological calcifications in the heart, the calcium may be a deposit of calcium salts within the heart tissue, or it might occur as a precipitate, as is found in the endocardium. The deposition of calcium salts within the heart takes place only in dead, or markedly deteriorated, never in healthy tissue. The process begins with the deposit of fine calcium granules, usually calcium phosphate, within the broken up heart muscle fibers. These granules then gradually coalesce, forming plaques, and gradually involve all of the elements of the heart. The ultimate cause of the phenomenon seems to lie in the factors controlling the calcium tolerance of the cell and in the nature of the physiochemical processes within the individual cell.

It is interesting to consider the question as to why Nature has formed true bone in this calcified tissue in the heart. It is possible that such bone would serve the heart more effectively than amorphous or crystalline calcium in preventing a rupture of the weakened heart muscle for the bone trabeculae may be laid down with reference to stress and lines of force. Further, we may ask as to the origin of the osteoclasts and osteoblasts which has never been definitely settled. The occurrence of these cells would suggest the possible correctness of the belief of Wingate Todd that the osteoblasts are fibroblasts or connective tissue cells which have undergone certain characteristic modifications. Certainly, the change from calcium deposit to true bone formation suggests that an attempt is being made to specialize the cells and produce a working tissue, a process seen in life phylogenetically and ontogenetically.

The diagnosis of cardiac aneurysm is seldom made, although from Parkinson's study⁴ aneurysm followed infarction in 9 per cent of the cases. Our case would have escaped attention if roentgenographic study had not been requested. In all cases of heart disease, roentgenographic study should be made. In order to detect conditions which would otherwise escape the attention of pathologists, Scholz roentgen-rays all specimens routinely at postmortem examination.

It is also of interest¹ that our patient lived 21 years after his infarction, 19 of those 21 years without the knowledge of or symptoms of heart disease. Furthermore, his recovery followed only 18 days of rest in bed. Although it probably takes six or eight weeks for fibrous replacement of infarcted heart tissue, 18 days of rest were sufficient in this instance, suggesting how great are the recuperative powers of the heart.

The author wishes to thank F W Mackoy, W F Ragan, J E Habbe, and Norbert Enzer, physicians, for their help in the study of this patient, and Mr Leo C Massopust, Marquette University, who prepared all the illustrations.

BIBLIOGRAPHY

- 1 GROEDEL, F M. Reste Mitteilung ueber die Differenzierung einzelner Herzhochlen im Roentgenbilde und den Nachweis von Kalkschatten i d Herzsilhouette intra vitam, Fortschr a d Geb d Rontgenstrahlen, 1911, xvi, 337
- 2 SCHOLZ, THOMAS. Calcification of the heart its roentgenologic demonstration, Arch Int Med, 1924, xxxiv, 32-59
- 3 COHEN, JACOB N, and LEVINE, HARRY S. Calcification of myocardium with bone formation report of a case, Arch Int Med, 1937, lx, 486-494
- 4 PARKINSON, JOHN, BEDFORD, D EVAN, and THOMSON, W A R. Cardiac aneurysm, Quart Jr Med N S, 1938, vii, 455-478
- 5 WHITE, PAUL D. Heart disease, 1931, The Macmillan Company, New York

EDITORIAL

EPIDEMIC KERATOCONJUNCTIVITIS

This disease, which first appeared in epidemic form in the United States in California and Oregon in 1941, has become so widely distributed in this country that it constitutes a serious menace by reason of the disability it causes among workmen as well as the visual impairment suffered by some of its victims. The present outbreak was preceded by an epidemic in Hawaii in 1940, from which it was presumably brought to San Francisco where it caused an extensive epidemic among shipyard workers. Good clinical descriptions of the disease have been published by Hogan and Crawford¹ in San Francisco, by Rieke² in Oregon, and by Sanders et al³ in a smaller group of cases in New York.

The disease is conveyed from one person to another by direct contact, but it appears as a rule not to be highly contagious. Transmission to other members of a family occurs occasionally but is not the rule. Working in close contact under unhygienic conditions seems to favor its spread. Minor injuries to the eye and other types of inflammation are thought by some to be important predisposing factors.

After an incubation period of about five to 12 days, the patient complains of burning in one eye, often of a foreign body in the eye. The eye shows signs of an acute conjunctivitis, first limited to the lids, especially the lower lid. There is intense congestion, chemosis and edema which later extend to the bulbar conjunctiva. In severe cases a pseudomembrane may form, removal of which leaves small bleeding spots. A striking feature is the scantiness of the exudate which is mucoid or watery, never purulent, and contains lymphocytes. Smears and cultures from the exudate are sterile or show no organisms of significance, and no inclusion bodies.

The conjunctivitis may be preceded by mild systemic symptoms, headache, pain over the infected eye, slight fever and malaise, regularly so in severe cases. In a large majority of the cases the preauricular lymph nodes are enlarged and tender, occasionally also the submentals and upper cervicals.

In about half the cases the second eye becomes involved after a few days, but the inflammation is usually less intense. Simultaneous involvement of both eyes is rare.

After about one to two weeks (2 to 38 days) keratitis appears in from 50 to 85 per cent of the cases, often accompanied by pain, photophobia and lacrimation. Slight degrees of involvement may be missed unless repeated

¹ HOGAN, M. J., and CRAWFORD, J. W. Epidemic keratoconjunctivitis (Superficial punctate keratitis, keratitis subepithelialis, keratitis maculosa, keratitis nummularis), *Am Jr Ophth*, 1942, xxv, 1059-1078.

² RIEKE, F. E. Epidemic conjunctivitis of presumed virus causation, *Jr Am Med Assoc*, 1942, cxix, 942-943.

³ SANDERS, M., GULLIVER, F. D., FORCHHEIMER, L. L., and ALEXANDER, R. C. Epidemic keratoconjunctivitis, *Jr Am Med Assoc*, 1943, cxxi, 250-255.

examinations are made with a slit lamp. The keratitis may be limited to one eye, or as in 28 of Sanders' 42 cases with keratitis, the second eye may become involved a few days after the first. The keratitis manifests itself by the appearance of small grayish discrete spots about 0.5 mm in diameter, which may coalesce to form larger areas. The spots may be sparse or very numerous, are chiefly in the exposed portions of the cornea, and are more numerous in the central pupillary area than in the periphery. They are located in the superficial portion of the substantia propria beneath Bowman's membrane. Herpetiform vesicles or superficial ulcerations which stain with fluorescein are very rare, and corneal sensation is usually retained. Vascularization never occurs. Once formed, these infiltrates are often very persistent. The keratitis may continue in an acute form and disability may persist for as long as eight weeks. In Sanders' series, in 71 per cent of the cases there was disability lasting from one to eight weeks.

In some of the reported cases the infiltrates gradually disappeared after from one week to several months, but in many cases they persisted for from six months to two years, and in some presumably they will be permanent.

The degree of visual impairment has varied in different epidemics. Sanders reported that in one-third of the cases with keratitis there was a loss of vision of from 5 to 15 per cent. Others have reported greater impairment, from 20/55 to 20/66. Hogan and Crawford reported that in most cases with visual impairment, 20/30 vision was regained within about three months. Such a degree of visual loss, however, may last many months and probably will be permanent in some cases. Many patients complain of halos especially about bright artificial lights. Complete loss of useful vision, however, rarely if ever occurred, and scars have formed only in rare cases in which there had been superficial abrasions of the cornea.

Until recently the cause of the disease was unknown. There has been general agreement that it is not a bacterial infection. Sanders and his associates,^{4, 5} however, have obtained strong evidence that the agent is a filterable virus. By inoculation of material from the eye of two human cases intracerebrally into white mice, they succeeded in producing an infection which could be propagated only through a short series of mice. However, if ground up brain tissue from an infected mouse was inoculated into a tissue culture medium composed of embryonic mouse brain and serum ultrafiltrate multiplication of the virus occurred, and there was an enhanced virulence for mice, so that infection by intracerebral inoculation was uniformly fatal and the virus could be maintained indefinitely. Young unweaned mice could be infected also by intraperitoneal injection. Rabbits also could be infected by intracerebral inoculation, but rats and guinea pigs were resistant. One human volunteer was infected by inoculation into the conjunctiva, and infection was apparently produced in a similar manner in two monkeys. The

⁴ SANDERS, M. Epidemic keratoconjunctivitis (Shigwan conjunctivitis): Isolation of a virus, *Arch. Ophthalm.*, 1942, XXXI, 581-586.

⁵ SANDERS, M. and ALFANDER, R. C. Epidemic keratoconjunctivitis: Isolation and identification of a filterable virus, *Jr. Exper. Med.*, 1943, LXXX, 71-81.

virus passed readily through Berkefeld and Seitz filters, and through colloidion membranes with a pore diameter of 75 millimicra

By intraperitoneal injection of serum-virus mixtures into unweaned mice, Sanders was able to demonstrate protective substances in the serum of convalescent patients. In seven cases, including the experimentally infected volunteer, they demonstrated protective substances in individuals whose serum had been inactive in the acute stage of the disease. By suitable crossed protection tests they demonstrated the identity of the two strains of virus isolated. The serum of convalescent patients in California protected mice from the virus strains isolated from cases in New York. They also demonstrated that this virus was immunologically distinct from that of lymphocytic choriomeningitis, of Theiler's spontaneous mouse encephalomyelitis, and of ordinary herpes. It seems highly probable, therefore, that this virus is the specific causative agent of the disease.

Although this disease is new to most physicians in this country, many reports of similar epidemics have been published. Although it is impossible now to prove that the etiological agent in these epidemics was immunologically identical with Sanders' virus, the clinical descriptions are essentially identical with those of the present epidemic. One of the best early descriptions is that of Fuchs,⁶ who reported 36 cases. He described the initial conjunctivitis with catarrhal nonpurulent exudate, the late appearance of the keratitis, as the conjunctivitis was subsiding, the development of 'punctate' opacities 0.5 mm or more in diameter beneath Bowman's membrane, without superficial ulcerations, and the protracted course with frequent persistence of the opacities for six months to a year. Many descriptions of similar epidemics appeared in the German literature from 1938 to 1941.⁷

Among others reporting similar epidemics may be mentioned Heibert, 226 cases from Bombay in 1901, Wright, 3500 cases from Madras in 1930, Doggert, 44 cases from London in 1933, Ling, an epidemic in China in 1936, Houwer, in Java in 1938, Hamilton, in Tasmania in 1941, and Viswalingen, 3500 cases in Malaya in 1941. Hobson in 1938 reported 16 cases in a veterans' hospital in San Francisco. The disease, therefore, is not altogether new in the United States.

The disease is self-limited, but no form of treatment has been shown to influence its course. Strong antiseptic solutions are injurious. Sulfathiazole locally has not been definitely helpful. Braley and Sanders⁸ in a small uncontrolled series of cases reported promising results from the intravenous administration of 20 to 50 cc of convalescent serum. This procedure merits further trial, but the evidence supporting it is still very meager.

⁶ FUCHS, E. *Keratitis punctata superficialis*, *Wien klin Wchnschr*, 1889, 11, 837-841.

⁷ SMETMANS, F. K., et al. *Aussprache über die Keratokonjunktivitis epidemica*, *Med Klin*, 1939, xxxv, 235-237.

⁸ BRALEY, A. E., and SANDERS, M. *Treatment of epidemic keratoconjunctivitis*, *Jr Am Med Assoc*, 1943, cxxxi, 999-1000.

Although there is some dispute as to the degree of contagiousness of the disease, there is no doubt that it is conveyed by direct contact. The only practicable means now available to limit spread of the infection is isolation of the patient at the onset of the infection. Since it is difficult or impossible to make a definite diagnosis at this time, it will be necessary to exclude from work every individual with an inflamed eye until a positive diagnosis can be made or until the inflammation has subsided. Although such measures seem drastic, they appear indispensable if serious interruptions of work schedules are to be avoided. Meticulous asepsis on the part of examining physicians is equally imperative.

.

REVIEWS

Anoxia, Its Effect on the Body By EDWARD J VAN LIRF, Ph D, M D 269 pages; 23 × 15.5 cm The University of Chicago Press, Chicago, Illinois 1942 Price, \$3.00

This is a carefully composed analytical monograph on the subject of anoxia, written by an eminent investigator, and represents an epitome of the important contributions to our knowledge of this subject

It evidences a complete and meticulous search of the existing literature, is completely authenticated, and, through the author's suggestions often found at the end of each section, should provide investigators in these problems a rich source of suggestions for further research

Little detailed or technical data are given and illustrations are few, but the material has been so edited that essential facts are not distorted The excellent footnotes and index render this work applicable as a source-book The clarity and straightforward manner in which the information is presented provides the internist or flight surgeon with a valuable source of basic knowledge

J A W

Gynecologic Surgery By MORRIS A GOLDBERGER, M D, F A C S 164 pages, 22 × 14 cm Oxford University Press, New York City 1942 Price, \$2.00

As Dr Goldberger states in the preface, "this cannot replace the full standard text books of Gynecology," but there is definitely a place for this outline in the library of every student and specialist The outline is logical in its approach, and reflects the author's keen mind and ability The procedures recommended have all been carefully selected and have stood the test of time

The brief outline of the anatomy and pathology should be helpful to both students and practitioners The blank pages are a feature which should be incorporated in more books

In general it is an excellent book

W K D

BOOKS RECEIVED

Books received during March are acknowledged in the following section As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them

Brucellosis in Man and Animals Revised Edition By I FOREST HUDDLESON, D V M, M S, Ph D Contributing authors A V HARDY, M S, M D, Dr P H, J E DEBONO, M D, M R C P, and WARD GITTNER, D V M, M S, Dr P H 379 pages, 23 × 16 cm 1943 Commonwealth Fund, New York, N Y Price, \$3.50

Doctor in the Making By A W HAM, M B, and M D SALTER, M A, Ph D 179 pages, 20 × 13.5 cm 1943 J B Lippincott Co, Philadelphia Price, \$2.00

Behind the Sulfa Drugs By IAGO GALDSTON, M D 174 pages, 19.5 × 13 cm 1943 D Appleton-Century Co, New York, N Y Price, \$2.00

Vascular Spasm—Experimental Studies By ALEXANDER JOHN NEDZEL, M.D, M S 151 pages, 27.5 × 19.5 cm 1943 University of Illinois Press, Urbana, Illinois Price, \$2.75 (clothbound), \$2.25 (paperbound)

- Chemotherapy of Gonococcic Infections* By RUSSELL D HERROLD, B S M D 137 pages, 25 × 17 cm 1943 C V Mosby Co., St Louis, Missouri Price, \$3 00
- Contribucion al estudio anatomico clinico de las afecciones del endocardio* Tesis de doctorado por el Dr MANUEL PEREA MUÑOZ 363 pages, 27 × 18 5 cm 1942 Universidad Nacional de Buenos Aires—Facultad de Ciencias Medicas
- Tables of Food Values* Revised and Enlarged Edition By ALICE V BRADLEY, M D 224 pages, 25 5 × 20 cm 1943 Manual Arts Press, Peoria, Illinois Price, \$3 50

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,364 Fellows and Associates of the College on active military duty. Herewith are reported the names of 48 additional members, bringing the grand total to 1,412.

Glen I. Allen

Walter F. Berberich

William L. Bettison

Philip B. Bleecker

J. Russell Brink

Frederick S. Bruckman

George B. Craddock

Herbert D. Edger

Frederick A. Eigenbrod

George F. Ellinger

Marcel J. Foret

Julian M. Freston

John E. Garcia

Charles C. Gill

Bernard A. Goldman

Abraham M. Gordon

Edwin M. Goyette

Russell B. Hanford

Thomas J. Hanlon

J. Watson Harmer

Ferdinand C. Helwig

Kelse M. Hoffman

Joseph L. Hollander

Willard F. Hollenbeck

Charles A. Jones

Murrel H. Kaplan

Andrew J. Klein

Rudolph A. Kocher

Milton L. Kramer

Isadore J. Kwitny

Alan N. Leslie

Roscoe F. Millet

Marshall G. Nims

Alexander P. Ormond

George M. Powell

Charles J. Roberts

Robert B. Skinner

Hyman A. Slesinger

William Stein

Joseph B. Stevens

Paul S. Strong

Paul R. Swanson

Charles M. Thompson

Arie C. van Ravenswaay

Stoughton R. Vogel

Clarence B. Whims

Major S. White

Willard H. Willis

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. V. Thomas Austin, Urbana, Ill.

Dr. Seymour Fiske, New York, N. Y.

Dr. Herbert T. Kelly, Philadelphia, Pa.

Dr. John T. Murphy, Toledo, Ohio

Dr. Harold Orr, Edmonton, Alta.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

Dr Ernest E Irons, F A C P, Chicago, Ill—"The Last Illness of Sir Joshua Reynolds" and "Theophile Bonet, 1620-1689,—His Influence on the Science and Practice of Medicine",

Dr Peter J Steincrohn, F A C P, Hartford, Conn—"Heart Disease Is Curable"

Reprints

Dr Daniel M Brumfiel, F A C P, Saranac Lake, N Y—7 reprints,

Dr Richard M Burke, F A C P, Oklahoma City, Okla—1 reprint,

Abraham G Cohen (Associate), Major, (MC), U S Army—1 reprint,

Joseph H Delaney (Associate), Captain, (MC), U S Army—1 reprint,

Charles A Flood, F A C P, Major, (MC), U S Army—3 reprints,

Dr Murray B Gordon, F A C P, Brooklyn, N Y—13 reprints,

Dr Andrew C Ivy, F A C P, Chicago, Ill—1 reprint,

R Harold Jones, F A C P, Major, (MC), U S Army—2 reprints,

Dr William G Leaman, Jr, F A C P, Philadelphia, Pa—3 reprints,

Dr Francis M Pottenger, Jr, F A C P, Monrovia, Calif—1 reprint,

Dr Richard Kohn Richards (Associate), North Chicago, Ill—10 reprints,

Dr Michael W Shutkin (Associate), Milwaukee, Wis—2 reprints,

Dr William C Voorsanger, F A C P, San Francisco, Calif—1 reprint

Dr Israel M Rabinowitch, F A C P, Montreal, Que, has donated to the College Library of Publications by Members a set of seven manuals on Chemical Warfare, which he prepared for the Office of the Director of Civil Air Raid Precautions

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE
William A Werrell, M D, Assistant
Secretary
1301 University Ave
Madison, Wis

Written Examinations Will be given in various cities and a number of Army and Naval stations, October 18, 1943 Applications must be filed before September 1

Oral Examinations Philadelphia, Pa, May 26-29, 1943, Chicago, Ill, June 9-11, 1943, New Orleans La. and San Francisco, Calif, dates to be announced later Oral examinations for certification in the sub-specialties, Allergy, Cardiovascular Disease Gastroenterology, and Tuberculosis will be held in conjunction with the oral examinations in internal medicine

AMERICAN BOARD OF DERMATOLOGY AND
SYPHILOLOGY
C Guy Lane, M D, Secretary
416 Marlboro St
Boston, Mass

Written Examinations Will be given in various cities, September 27, 1943

Oral Examinations Philadelphia, Pa, November 5-6, 1943

AMERICAN BOARD OF PATHOLOGY.
F W Hartman, M D, Secretary
Henry Ford Hospital
Detroit, Mich

Written and Oral Examinations Chicago, Ill, June 2-3, 1943

AMERICAN BOARD OF PEDIATRICS
C A Aldrich, M D, Secretary
707 Fullerton Ave
Chicago, Ill

Written Examinations: Will be given in various cities, October 8, 1943
Oral Examinations New York, N Y, November 20 or 21, 1943

AMERICAN BOARD OF PSYCHIATRY AND
NEUROLOGY:
Walter Freeman, M D, Secretary
1028 Connecticut Ave, N W
Washington, D C

Written Examinations Dates and place will be announced later
Oral Examinations New York, N Y, probably December 20-21, 1943

AMERICAN BOARD OF RADIOLOGY
B R Kirklin, M D, Secretary
Mayo Clinic
Rochester, Minn

Oral Examinations Chicago, Ill, June 3-5, 1943

For further information and application forms communicate with the respective secretaries

A C P REGIONAL MEETING FOR MONTANA AND WYOMING

A Regional Meeting of the American College of Physicians for the States of Montana and Wyoming was held in Great Falls, Montana, May 1, 1943, under the direction of Dr Ernest D Hitchcock, F A C P, College Governor for Montana. The scientific program of the meeting was as follows

MORNING SESSION

Presiding Officer

DR GEORGE E BAKER, F A C P

Casper, Wyo

"Water Balance in Consideration of Edematous Patients"—Dr F R Schemm, F A C P, Great Falls, Mont

"Factors in Prognosis in Coronary Disease, Old Hearts Under the Strain of War"—Dr Harold W Gregg, F A C P, Butte, Mont

"Glycosuria, Blood Sugar Curves"—Dr A R Foss, F A C P, Missoula, Mont

"Chemo-Prophylaxis"—Dr Thomas F Walker, F A C P, Great Falls, Mont

AFTERNOON SESSION

Presiding Officer

DR ERNEST D HITCHCOCK, F A C P

Great Falls, Mont

"Rocky Mountain Spotted Fever"—Dr George E Baker, F A C P, Casper, Wyo

"Air Evacuation of Battle Casualties"—Scott M Smith (by invitation), Lieutenant Colonel, (MC), U S Army

"Yellow Fever Prophylaxis"—Dr M V Hargett, F A C P, U S Public Health Service, Hamilton, Mont

"The Use of the Blood Groups in the Tracing of Racial Origins and Migrations"—P B Candela (by invitation), Lieutenant, (MC), U S Army

"Allergy in General with Special Reference to Newer Developments"—Dr. M A Shillington, F A C P, Glendive, Mont

"Management of the Menopause with Special Reference to the Newer Synthetic Estrogens"—Dr Earl L. Hall (by invitation), Great Falls, Mont

This meeting concluded with a dinner meeting in the evening at which Dr William G. Richards, F A C P, Billings, Mont, spoke on "Hyperthyroid and the Neurotic as Illustrated by Shakespeare's Characters of Macbeth and Hamlet" and John L. Slattery, Attorney-at-Law, Great Falls, Mont, on "Some Observations"

Under the auspices of the Carlos Finlay Institute of the Americas and with the co-operation of the American Medical Association, the American College of Physicians, the American College of Surgeons, the American Drug Manufacturers Association, the American Hospital Association, the American Pharmaceutical Manufacturers Association, the American Pharmaceutical Association, the American Surgical Trade Association, the Wholesale Surgical Trade Association, and the National Physicians Committee, the National Conference on Planning for War and Post War Medical Services was held in New York, N Y, Monday, March 15 1943. Dr James E. Paulin, F A C P, President of the College, Atlanta, Georgia, presided at the morning session and Fred Rankin, Brigadier General, (MC), U S Army, President of the American Medical Association, presided at the afternoon session. Among the Fellows of the College who participated in the program were

Thomas T. Mackie, F A C P, Lieutenant Colonel, (MC) U S Army—"War and the Migration of Tropical Diseases",

Dr John B. Youmans, F A C P, Nashville, Tenn—"Nutritional Diseases as a Post War Problem"

On September 29, 1942, the War Department acquired the Greenbrier Hotel at White Sulphur Springs, W Va, and has designated it as the Ashford General Hospital in honor of the late Bailey K. Ashford, F A C P, Colonel, (MC), U S Army.

Colonel Ashford was born in Washington, D C, in 1873, and entered the Medical Corps of the U S Army in 1897. In 1910 he was a delegate to the International Congress of Industrial Hygiene and Alimentary Hygiene in Brussels. In 1917 he sailed with the First Division for France and later became Chief Surgeon of the Sixth Army Corps. After the war he was transferred to the General Staff in Washington and was made Editor-in-Chief of the Official Medical History of the War. Colonel Ashford was awarded many signal honors. A few of these were the Distinguished Service Medal, the Order of St Michael and St George of England, the Order of the Nile of Egypt, and degrees of Doctor of Science from the Universities of Georgetown, Columbia, Egypt and Puerto Rico. Colonel Ashford became a Fellow of the American College of Physicians on March 10, 1923, and served as College Governor of Puerto Rico for many years.

On March 21, 1943 James S. Simmons, F A C P, Brigadier General, (MC) U S Army, delivered the commencement address at the special graduation exercises for the Washington University Schools of Medicine, Dentistry and Nursing at St Louis, Mo. General Simmons spoke on "New Horizons in Military Medicine."

Dr Jacob C. Geiger, F A C P, San Francisco, Calif, was recently given the award of Fellow and "Member Correspondiente" of the National Academy of History of Panama.

The honor was granted upon recommendation of the Hon. the Director of the Education of Panama and approved by the President of the Academy on February 15 1943. The award was accompanied by a diploma, an honorary degree and citation "For your relevant personal and scientific contributions in public health and service to Panama."

At a recent meeting of the Medical Board of the Philadelphia General Hospital, Philadelphia, Pa, Dr Russell S Boles, F A C P, was elected President, Dr Samuel B Hadden, F A C P, Secretary, and Dr. Lauren H Smith, F A C P, Treasurer

Harold J Harris, F A C P, Lieutenant Commander, (MC), U S Naval Reserve, spoke on "Biucellosis Its Diagnosis, Differential Diagnosis and Treatment" at one of the Friday Afternoon Lectures of the New York Academy of Medicine, March 19, 1943

Dr Louis L Peikel, F A C P, Jersey City, N J, Dr Sigurd W Johnsen, F A C P, Passaic, N J, and Dr Hyman I Goldstein (Associate), Camden, N J, participated in the scientific program and discussions at the March meeting of the New Jersey Gastro-enterological Society held in Glen Ridge

Ellis H Hudson, F A C P, Lieutenant Commander, (MC), U S Naval Reserve, recently delivered a series of four lectures at the Mayo Clinic, Rochester, Minn, on malaria and other tropical diseases

Dr Richard Kohn Richards (Associate), North Chicago, Ill, addressed a meeting of the Society for Experimental Biology and Medicine in Chicago on March 9, 1943 Dr Richards spoke on "The Role of Liver and Kidney in the Action of Dicumarol"

Under the Presidency of Dr Joseph D McCarthy, F A C P, Omaha, Nebr, the National Conference on Medical Service held its 17th Annual Meeting in Chicago, Ill, February 14, 1943

Dr David J Davis, F A C P, will retire September 1, 1943, as Professor and Head of the Department of Pathology, Bacteriology and Public Health and as Dean of the University of Illinois College of Medicine, Chicago Dr Davis has been associated with the Medical School for twenty-nine years and was named Professor of Pathology in 1914 and Dean in 1925

The 92nd Annual Session of the Iowa State Medical Society was held in Des Moines April 29-30, 1943 Among those who participated in the program were

Dr Harry L Smith, F A C P, Rochester, Minn—"Coronary Disease Its Recognition and Management",

Dr James A Greene, F A C P, Iowa City, Iowa—"Tropical Medicine in Iowa in the Postwar Era",

Dr Christian B Luginbuhl, F A C P, Des Moines, Iowa—"Acute Pulmonary Conditions Simulating Abdominal Disorders"

Dr Lee R Woodward, F A C P, Mason City, President-Elect of the Society, delivered an address at the annual banquet

Dr Herman H Riecker, F A C P, Ann Arbor, Mich, spoke on "Heart Disease in Industry" at a Postgraduate Industrial, Medical and Surgical Conference held in Detroit, Mich, April 8, 1943, under the auspices of the Committee on Industrial Health of the Michigan State Medical Society and the Department of Postgraduate Medical Education of the University of Michigan

Dr Cornelius P Rhoads, F A C P, New York, N Y, delivered the 9th Harrison Stanford Martland Lecture of the Essex County Anatomical and Pathological

Society of the Academy of Medicine of Northern New Jersey in Newark on March 17, 1943 Dr Rhoads spoke on "Cancer and the Rôle Played by Vitamins and Endocrines"

On February 5, 1943, Dr Harrison F Flippin, F A C P, Philadelphia, Pa, gave a Mayo Foundation Lecture in Rochester, Minn, on the "Management of Pneumonia"

Dr George W Thorn, F A C P, Boston, Mass, gave the annual Alpha Omega Alpha Lecture at the Yale University School of Medicine, New Haven, Conn, February 11, 1943 The subject of Dr Thorn's lecture was "Clinical Aspects of Disturbances in Sodium Chloride Metabolism"

On April 23, 1943, Dr Chester M Jones, F A C P, Boston, Mass, delivered the 19th Lewis Linn McArthur Lecture of the Frank Billings Foundation, Chicago, Ill Dr Jones spoke on "The Relationship Between the Nervous System and Pain Perception with Particular Reference to the Gastrointestinal Tract"

The Northern Tri-State Medical Association held its annual meeting at Ann Arbor, Mich, April 13, 1943 Among the members of the College from the University of Michigan Medical School who participated in the program were

Dr Cyrus C Sturgis, F A C P—"The Clinical Significance of Leukopenia",

Dr Frank N Wilson, F A C P—"The Diagnosis and Treatment of Coronary Artery Disease",

Dr Herman H Riecker, F A C P—"Differential Diagnosis and Management of Hypertension",

Dr Richard H Lyons (Associate)—"The Management of the Edematous Patient",

Dr Arthur C Curtis, F A C P—"The Treatment of Tinea Infections"

Dr Irvine H Page (Associate), Indianapolis, Ind, spoke on "Essential Hypertension of Renal Origin" at a symposium on hypertension conducted at the annual meeting of the Hispanic-American Medical Society of New York March 23, 1943, in New York, N Y

At the 97th Annual Meeting of the Ohio State Medical Association held in Columbus, March 30-31, 1943 Dr Tom D Spies F A C P, Birmingham, Al spoke on "Importance of Optimum Nutrition for the Civilian Population in Wartime" and Dr John A Toomey, F A C P, Cleveland, Ohio spoke on "Importance of Immunization of the Civilian Population in Wartime"

Dr Walter F Donaldson, F A C P, Pittsburgh, Pa, was among those who addressed a session devoted to "Medicine and the War"

The Medical Association of the State of Alabama held its annual session in Birmingham, April 20-22, 1943 Among the speakers were

Dr James E Paullin, F A C P, Atlanta, Ga—"The Contribution of American Medicine to the War Effort",

Bartholomew W Hogan F A C P, Commander, (MC) U S Navy—"The Navy Medical Corps in Combat Areas"

Dr Alexander H Stewart, F A C P, Harrisburg has been reappointed Secretary of the Pennsylvania State Board of Health by the Governor

Dr Herbert T Kelly, F A C P, Philadelphia, Pa, presented a paper on "Nutrition—An Implement of the Physician" at a meeting of the Jefferson County Medical Society in Punxsutawney, Pa, April 8, 1943

The 13th Annual Health Institute of the Woman's Auxiliary of the Philadelphia County Medical Society was held April 13, 1943 "Our Own Health" was the theme of the program The following Philadelphia Fellows of the College contributed

Dr Truman G Schnabel—"Is It Kidney?",
 Dr Merle M Miller—"Influence of Allergy on Our Health",
 Dr Herbert T Kelly—"Our Changing Foods",
 Dr George C Griffith—"Care of the Heart—Normal and Abnormal "

Dr John H Musser, F A C P, New Orleans, La, spoke on "The Doctor's Heart" at the annual meeting of the Arkansas Medical Society in Little Rock, April 19-20, 1943

The 70th Annual Meeting of the Florida Medical Association was held in Jacksonville, April 15-16, 1943 Dr George Bachr, F A C P, Washington, D C, spoke on "British and American Experiences in Civil Defense" and Sanford W French, F A C P, Colonel, (MC), U S Army, spoke on "The Doctor in the War Effort"

Dr George W Thoin, F A C P, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass, was awarded the "Chancellor's Medal" at the recent graduation ceremonies at the University of Buffalo This medal is awarded annually by the University Council for "outstanding achievement"

Dr Raymond Hussey, F A C P, Baltimore, Md, spoke on "Occupational Diseases and Their Control" at a series of Industrial Health Institutes on the Conservation of Manpower conducted in Augusta, Savannah, Atlanta and Columbus, Ga, March 11-16, 1943 The program was sponsored by the Medical Association of Georgia, the Georgia Department of Health and the Associated Industries of Georgia

Dr Joseph F Bredeck, F A C P, St Louis, Mo, conducted a discussion on syphilis and Drs Carl V Moore, Jr, F A C P, and Raymond O Muether, F A C P, also of St Louis, conducted a discussion on transfusions, at the annual session of the Missouri State Medical Association in St Louis, April 18-20, 1943

Dr Harold W. Stevens, F A C P, Middleboro, was recently elected President of the Massachusetts Public Health Association

On February 16, 1943, the General Electric X-Ray Corporation, Chicago, Ill, was awarded the coveted Army-Navy "E" for high achievement in war production

Dr Cyrus C Sturgis, F A C P, Ann Arbor, Mich, gave the dedicatory address at the ceremonies dedicating the Institute of Medical Research at the Toledo Hospital, Toledo, Ohio, March 27, 1943 Dr Sturgis spoke on "The Future of Medical Research"

The Institute for Medical Research was made possible by an endowment from the late Frank Collins of the National Supply Company of Toledo The Institute

will maintain interest in diseases in general, depending upon the availability of the personnel and will not be devoted to the study of any single disease

Dr Clarence E de la Chapelle, F A C P, New York, N Y, spoke on the "Treatment of Coronary Thrombosis" at a joint meeting of the Philadelphia Health Association and the Section on Medicine of the Philadelphia College of Physicians, May 10, 1943

Dr William S McEllroy, F A C P, Pittsburgh, Pa, spoke on the 'Effect of the Army and Navy Collegiate Program on Medical Education' at a meeting of the Pittsburgh Surgical Society, March 25, 1943

RETURN AND PAYMENT OF VICTORY TAX BY EMPLOYERS

Employers are required to withhold the 5% Victory Tax on employees' wages in excess of \$12 00 per week, and must make a return and transmit the tax quarterly to the Collector of Internal Revenue having jurisdiction, April 30, July 31, October 31 and January 31, using form V-1, Return of Victory Tax Withheld. This form may be obtained from the collector's office, and must be signed and sworn to by the employer. Duplicates of form V-2, receipt given employees, should be made and filed with the final report at the end of the year, on or before January 31 1944. Because of severe penalties prescribed, physicians should make prompt returns on all tax withheld at the times designated.

WAR-TIME GRADUATE MEDICAL MEETINGS

By joint action of the American College of Physicians, the American Medical Association and the American College of Surgeons, an organization has been effected under the title of "War-Time Graduate Medical Meetings." Commander Edward L Bortz, (MC), U S N, of Philadelphia, is the appointee of the American Medical Association and has been appointed Chairman. Dr William B Breed of Boston is the appointee of the American College of Physicians and Dr Alfred Blalock, Baltimore, is the appointee of the American College of Surgeons.

After study of methods whereby medical authorities might be utilized in an educational program for the benefit of doctors in the armed services. Officials of the American Medical Association, American College of Surgeons and American College of Physicians have appropriated the sum of \$20,000 and appointed a committee of three, one man from each organization to proceed with the work of organization and action.

The program is essentially an elaboration of a teaching plan that has been used successfully in the Boston, Chicago and Philadelphia areas originated by the American College of Physicians. It was so successful, in a limited way, that many requests have been received for its presentation on a national scale. In no way are the proposed courses to displace any of the educational activities now being carried on by the Officials of the Army and Navy medical services. The program has the approval and is authorized by, Surgeon General James C Magee, Surgeon General Ross T McIntire and Surgeon General Thomas Parran.

The teaching schedule will include ward walks, clinics, practical demonstrations, moving pictures, lectures and conferences offered to medical institutions throughout the entire nation.

In carrying out the plans of the Committee, no single pattern can be followed. However, suggested methods of approach are herewith listed.

(a) Meetings such as those already held in Boston, Philadelphia, etc.

where lecturers addressed groups in various camps on successive nights Or, a one-day meeting at a central point with several outstanding speakers embracing topics of vital interest

(b) The organization of teams which may arrange to visit one or more camps in nearby areas to put on a one-day and evening program Such teams may appear at two or three adjacent camps on successive days

(c) In areas where five or six service hospitals are within reasonable distance from a central distributing center, a complete six-day postgraduate program may be offered on the following basis:

The organization of six teams of two or more authorities each, from different medical specialties, to appear at the five or six hospitals in that area, each team on one particular day for five or six consecutive weeks The program may include teaching ward rounds and laboratory demonstrations for small groups in the morning hours Motion picture exhibits and one lecture with a question and answer period may be presented in the afternoon and a further lecture, seminar or round table conference in the evening

It is evident that any of the above plans, all of which are tentative and illustrative only, might have to be modified to meet local conditions However, teams of teachers should be available in the various medical concentration areas throughout the country to conduct full courses of instruction, where needed Also, it may be expedient, at occasional intervals, to repeat this circular or peripatetic plan two or even three times per year, depending on the change of medical personnel in the service hospitals

For organizational purposes, the country has been divided into 24 sections and key committees of three men appointed in each section to carry on the details of the program Likewise, to insure a most worthwhile program, a group of qualified authorities is needed to serve as National Consultants in the various special fields

The duties of the Section Committees are

- 1 To be responsible for the details of programs at each Service hospital in their respective regions, where programs are to be conducted,
- 2 To be responsible for the selection of teachers and speakers, with the assistance of the Central Committee and of the National Consultants,
- 3 To arrange time of meetings and schedules for travel and appearance of the teachers within their respective territories,
- 4 To furnish copies of the program to the Commanding Medical Officers of the hospitals (programs shall be mimeographed or otherwise reproduced by the hospitals themselves),
- 5 Supervision of expenses, which shall be limited to necessary travel costs, also the forwarding of statements of same to the Secretary of the Central Committee, Dr William B. Breed,
- 6 To obtain from the Commanding Officers at the end of the period of instruction a written statement concerning their impressions, and those of their staff, regarding the value of the courses, and suggestions for improvement

The duties of the Consultants are

- 1 Each Consultant to prepare a specimen six-hour teaching schedule, similar to the enclosed, which was prepared by Dr Edward A. Strecker in the field of psychiatry,
- 2 To cooperate with the regional committees in working out local programs and securing the teachers

When the teaching schedules have been prepared by the Consultants, and lecturers assembled, the programs will be submitted to the Surgeons General of the Army, Navy and Public Health Services and the Commanding Officers of the various Army Corps Commands and Naval Districts When the desire for courses is in-

licated, the details will be arranged through the local committee with the assistance of the key schedules and the appointment of speakers

It is the desire of the organizations in charge to extend to the doctors in the armed services the best facilities of American medicine in the interest of our fighting men

SPECIAL NOTICES

OFFICE OF CIVILIAN DEFENSE
Washington, D C
March 30, 1943

PENNANT TO IDENTIFY VEHICLES IN BLACKOUT

A uniform system of identification of emergency vehicles to enable them to operate during real or practice air-raid alarms was announced by the Office of Civilian Defense in Operations Letter No 111, which is a supplement to Operations Letter No 97

The primary identifying device is a white pennant measuring 18 inches along each side with a 6-inch basic Civilian Defense insignie, that is, the letters CD in red inside a white triangle superimposed on a red circle. The pennant is to be attached to the left front portion of the vehicle.

To identify emergency motor vehicles at night, the Operations Letter further prescribes a headlight mask to be used over the right headlamp. This mask may be made of any opaque material that can be easily, quickly, and securely fastened to the headlamp. It is intended for use where blackout regulations permit the use of headlights, in coastal dimout areas it should be used in conjunction with dimout equipment. The design of the mask embodies the "CD" insignie $2\frac{1}{2}$ to 3 inches in diameter in green.

Vehicles entitled to use the emergency identification include (a) vehicles of the armed forces of the United States or of her allies or other vehicles acting under orders or traveling with permission thereof, (b) vehicles of fire departments and governmental police agencies, (c) ambulances and rescue cars and other vehicles converted to such use in emergency services, (d) public utility repair vehicles operating in emergency service, (e) vehicles in emergency service as defined by State Civilian Defense authorities.

Use of the pennants and masks described was made mandatory for the 16 States and the District of Columbia in the Eastern Defense Command in an administrative order issued by the Director of Civilian Defense in accordance with the new Air Raid Protection Regulations which went into effect February 17. The Operations Letter recommends that all States adopt the definition of emergency motor vehicles and the methods of identification prescribed. Although many States have already adopted different methods of identifying emergency motor vehicles, it was urged that all States adopt the new devices. It was pointed out that a uniform system is particularly important in order that emergency motor vehicles which may be crossing State lines may not face unnecessary interference.

NURSES' AIDES FOR ARMY HOSPITALS

Volunteer Nurses' Aides trained under the joint program of the Office of Civilian Defense and the American Red Cross may now be used in Army hospital recruitment to announcements from the two agencies.

The Surgeon General of the Army has requested this service and the agencies have recommended that Nurses' Aides be assigned to Army general or station hospitals on request of the Commanding Officer of the hospital. They must receive their training in civilian hospitals as heretofore however, and Army hospitals must not interfere with supplying Aides to civilian hospitals.

agencies both now and in the event of enemy action, according to Medical Circular No 28, issued by Dr George Baehr, Chief Medical Officer, Office of Civilian Defense

This proposed extension of the services of Nurses' Aides emphasizes the need for increased effort in recruitment in localities which have not yet participated in the program, the Circular pointed out

CHANGES IN MEDICAL OFFICERS

Dr A William Reggio, Boston, recently State Chief of Emergency Medical Service for Massachusetts, has been appointed Regional Medical Officer for the First Civilian Defense Region, succeeding Dr Dudley A Reekie. Dr Reggio, a graduate of Harvard Medical School, was formerly an instructor in surgery at Harvard Medical School, assistant visiting surgeon, Massachusetts General Hospital, and consulting surgeon at the Massachusetts Eye and Ear Infirmary. The First Region includes the New England States.

Dr Reekie, who was assigned to the Central Office of the Medical Division in Washington in January as Acting Chief of the Field Casualty Section, has since been assigned by the Surgeon General of the U S Public Health Service to the U S State Department to head a group of Public Health Service officers who will act as special advisers on health matters to Robert Murphy, Chief Civil Affairs Officer for North Africa.

To succeed Dr Reekie as Acting Chief of the Field Casualty Section, Dr H van Zile Hyde, Regional Medical Officer for the Second Civilian Defense Region (New York, New Jersey and Delaware), has been transferred to Washington. Dr Hyde, formerly of Syracuse, New York, was the first Civilian Defense Regional Medical Officer appointed, having taken office in August 1941. Dr John J Bourke, deputy State Chief of Emergency Medical Service for New York, is now acting Regional Medical Officer for the Second Region.

Dr David D Rutstein, medical gas officer on the Washington staff, has resigned to become deputy health commissioner of New York City. Before he joined the Medical Division, Dr Rutstein was chief of the cardiac bureau of the New York State Health Department, Albany, New York.

TRANSPORTATION PLANS FOR CIVILIAN DEFENSE

Transportation for casualties from scenes of disaster to hospitals and for injured persons or other patients removed from Casualty Receiving Hospitals to Emergency Base Hospitals are included in plans for emergency transport service during war disasters, described in recent Operations Letters issued by the Office of Civilian Defense.

Plans for local transportation are centered in the Transport Officer of the U S Citizens Defense Corps. It is the duty of the Transport Officer to maintain inventories of local equipment that can be used by the various emergency services of the Citizens Defense Corps, and he is responsible for organization, training, and supervision of volunteer drivers' units. Such equipment may include passenger cars, station wagons, motorcycles, ambulances, and other private vehicles. The instructions provide, however, that ambulances and cars or trucks used as improvised ambulances, with their drivers, should be assigned regularly to the Emergency Medical Service and be under its direction.

Through joint action of the Office of Defense Transportation and the Office of Civilian Defense, concurred in by the War and Navy Departments, local commercial motor vehicles, including taxicabs and trucks of small operators, which are now under the jurisdiction of the Office of Defense Transportation, have been released to and also are available to the Transport Officer for local service in case of war emergency. He may make use of such vehicles immediately, without application to the ODT.

For transport facilities needed outside the local area, such as might be required

for evacuation of civilians or for transfer of injured persons to Emergency Base Hospitals in other cities or rural areas, the OCD and the ODT are cooperating in the organization of motor transport units in the larger common, contract, and private motor carriers of the critical areas of the country. These units, which will be trained in convoy service, will be provided by the ODT on request of the local Commander of the Citizens Defense Corps through the State Transport Officer and proper ODT district managers. ODT is at present developing an organization in the critical areas of the country under which its district managers will make contact with the local Transport Officers to make certain that each community is organized to function under the plan.

Operations Letter No 114, issued March 3, which describes the above arrangements, urges cooperative planning between the Citizens Defense Corps and such agencies as the American Red Cross, the Women's Defense and Ambulance Corps and local or State automobile associations or clubs, in order that several agencies may not seek to mobilize the same equipment and drivers independently, but may do so in cooperation. It is pointed out, for instance, that most local Red Cross chapters have permanent transportation committees to provide motor transport facilities for disaster relief. By cooperative planning, such facilities can be made available also to the Citizens Defense Corps.

The Executive Board of the Catholic Hospital Association of the United States and Canada is pleased to announce that under the patronage and by the invitation of His Excellency, the Most Reverend Hugh C Boyle, D D, Bishop of Pittsburgh, a Wartime Conference of the Association will be held at the William Penn Hotel, Pittsburgh, Pennsylvania, Friday to Monday, June 11th to 14th, 1943.

FOUR RESEARCH FELLOWSHIPS AVAILABLE THROUGH THE NEW YORK ACADEMY OF MEDICINE

The Committee on Medical Education of the New York Academy of Medicine, 2 East 103rd St, New York City, has been entrusted with the award of four fellowships of \$2,000 each for research in the following subjects:

- 1 The use of choline and other lipotropic factors in the prevention and treatment of fatty infiltration of the liver and hepatic insufficiency
- 2 The action of ingested choline, lecithin, methionine and inositol on precancerous lesions and disorders associated with neoplastic disease
- 3 The effects of riboflavin, certain amino acids, and casein on the development and growth of cancer
- 4 Study of the relationship between precancerous lesions of the mouth, hepatic insufficiency and gastrointestinal disorders

The funds for these Fellowships have been provided by Dr Charles Mayer, of New York City.

The Committee requests that research workers or laboratories engaged in studies along these lines or interested in research on these specified problems and who desire consideration by the Committee charged with awarding these fellowships, submit application for the desired award. This application should state the name of the individual who will conduct the research, the name of the laboratory or institution in which the work will be conducted, the special qualifications, interest or experience of the investigator and the institution which may justify the award. If the applicant has already conducted research in the specified field for which the award is sought, the fact should be stated and reprints of publication in this work be submitted. It should accompany the application together with any other facts or information of interest. An approval of the director of the laboratory should accompany the application if the application is not made by the director.

All applications should be sent in triplicate to Dr Mahlon Ashford, Secretary of the Committee, not later than October 30, 1943

REPORT. A C P NEW ORLEANS REGIONAL MEETING

The New Orleans Regional Meeting of the American College of Physicians, announced in the March issue of this Journal, was held on April 16-17

The program was conducted at the Charity Hospital and consisted of a group of clinics on Friday morning, a General Session on Friday afternoon, and a group of clinics and a clinical pathological conference on Saturday morning. The program was of a high order, with timely topics and prominent authorities from civilian practice, from the Medical Corps of the Army, the Medical Corps of the Navy and other agencies. Dr Edgar Hull, College Governor for Louisiana, was the General Chairman and the Governors of the participating States of Texas, Arkansas and Mississippi presided. A formal luncheon was held Friday noon, April 16, and was addressed by Comdr E L Bortz, (MC), U S N R, of Philadelphia, and by Col W Lee Hart, of the Medical Corps of the U S Army, Fort Sam Houston. There was a dinner meeting at the Roosevelt Hotel, Friday evening, April 16, at which Dr John H Musser was toastmaster. Addresses were made by Capt Bertram Groesbeck, Jr, an envoy of the Surgeon General, U S Navy, Pensacola, by Col Arden Freer, envoy of the Surgeon General, U S Army, Washington, and by E R Loveland, Executive Secretary of the College, Philadelphia.

Several of the important papers will appear in the ANNALS OF INTERNAL MEDICINE. The registration was considered excellent for a Regional Meeting, there being a total registration of 366, of which 139 were civilian physicians and 227 from the Army, Navy and Public Health Service.

REPORT A C P WASHINGTON, D C, REGIONAL MEETING April 24, 1943

The Regional Meeting of the American College of Physicians for the District of Columbia, Delaware, Maryland, Virginia, West Virginia and North Carolina, announced in the March issue of the ANNALS OF INTERNAL MEDICINE, was held as scheduled and was up to this time the most largely attended Regional Meeting of the College. 203 Fellows, 60 Associates and 200 guest physicians, most of whom were medical officers of the Armed Forces, making a total of 463, were in attendance. Of this total, 263 were Service doctors and 200 were civilian doctors. The District of Columbia led with 142 physicians, Maryland had 120, Virginia, 100, North Carolina, 28, West Virginia, 14, Delaware, 8, and there were 51 additional men from 18 States outside of the region.

The program was of outstanding excellence, and many of the papers will later appear in this journal.

The entire group were guests of the U S Naval Hospital at luncheon and in the evening a dinner meeting was held at the new Statler Hotel. Dr Wallace M Yater, Governor for the District of Columbia, was toastmaster. The meeting was addressed by President James E Paullin, Atlanta, Secretary-General George Morris Piersol, Philadelphia, Surgeon General Thomas Parran of the U S Public Health Service, Brigadier General Shelley U Marietta, Commanding Officer of the Walter Reed General Hospital, Rear Admiral Charles W O Bunker, Commandant of the U S Naval Medical Center, Brigadier General David N W Grant, Air Surgeon of the U S Army Air Forces, Brigadier General James S Simmons as personal representative of Surgeon General James C Magee of the U S Army, Commander Edward L Bortz, Chairman of the War-Time Graduate Medical Meetings, Philadelphia, and others.

OBITUARIES

DR CHARLES WALTER WADDELL

Dr Charles Walter Waddell, F A C P, for thirty-six years a prominent physician in Fairmont, West Virginia, died at his home on Coleman Avenue, Monday morning, March 29, 1943, at the age of sixty-five. Dr Waddell had been in declining health for more than a year, but continued to practice his profession until a few months ago when he was forced to relinquish his active duties, although his wise counsel and advice were sought thereafter by his patients and colleagues.

Dr Waddell was born in Preston County, West Virginia, November 24, 1877. He graduated from West Virginia University in 1900 with an A B degree, then taught for three years in the Fairmont schools. He was graduated in Medicine from Harvard Medical School in 1907, and had practiced his profession in Fairmont since, devoting his time to diagnosis and internal medicine.

Dr Waddell served his state and community in many ways. He was Chairman of the Advisory Board in World War I, was Consultant of the State Compensation Department and also of the Department of Public Assistance. He was very active in the Masonic and Elk Lodges.

In the year 1909 he married Miss Myrtle DeVene Shaw, a prominent singer of Fairmont. She survives him with three daughters.

Dr Waddell was past President of the Marion County Medical Society, represented his District as a Medical Councillor in the State Association for many years and was President of the West Virginia State Medical Association in 1938. He was elected to Fellowship in the American College of Physicians in 1922 and became a Life Member of the College in 1937.

An illustration of the esteem in which Dr Waddell was held in his home city is evidenced by the fact that the flag in front of the Fairmont General Hospital was placed at half mast when Dr Waddell's death was announced, also the Elk's flag and flags on other public buildings were lowered to half mast.

ALBERT H HOGG, M D, F A C P,
Governor for West Virginia

DR THEOPHILUS POWELL ALLEN

Dr Theophilus Powell Allen (Associate), New York, N Y, died at St Luke's Hospital on January 27, 1943. He was born in Milledgeville, Georgia, on July 24, 1896. His preliminary education was at the Georgia Military College and he graduated from this school with first honors and as Captain of his Company.

He then entered the University of Georgia at Athens, and while there entered the World War, volunteering as a Private in the Coast Artillery at Fort Screven, Georgia, in January, 1918. From Fort Screven he was sent

can Medical Association. He was also a Diplomate of the American Board of Radiology and has been an Associate of the American College of Physicians since 1939.

It is with sincere regret that the passing of Dr. Joseph Elward, a renowned doctor of medicine, is acknowledged.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HARRY MYRREL STEWART

Dr. Harry Myrrel Stewart, F.A.C.P., died August 28, 1942, at the age of 66. He was born at Frankstown, Pa., 1876, graduated from Jefferson Medical College of Philadelphia in 1905, and for many years was Radiologist at the Mercy, Conemaugh Valley Memorial and Lee Homeopathic Hospitals. Dr. Stewart was a former President of the Cambria County Medical Society and of the Pennsylvania Radiological Society, a member of the Medical Society of the State of Pennsylvania, American Roentgen Ray Society and the Radiological Society of North America. He was a Fellow of the American College of Physicians (1920) and of the American College of Radiology. During World War I he served as Captain in the Medical Corps of the U. S. Army.

DR. ISEDOR MACK UNGER

Dr. Isidor Mack Unger, F.A.C.P., of Ithaca, N. Y., died October 20, 1942, at the age of 65. Dr. Unger received his medical training at Bellevue Hospital Medical College, 1898, interned at the Montefiore Hospital, 1898-1900, and thereafter did postgraduate study at the New York State Pathological Institute. He was a veteran of the Spanish-American War and World War I. He was formerly District Consultant to the Bell Telephone Company of New York. For the past several years he had been Consultant to the Tompkins County Memorial Hospital, Visiting Physician to the Cornell University Infirmary, and Chairman of the Tompkins County Citizens Military Training Camp. He was a Colonel in the Medical Officers' Reserve Corps of the U. S. Army and was Chairman of the Five-County Medical Advisory Board No. 41, New York Selective Service.

Dr. Unger was a member and past President of the Tompkins County Medical Society, a member of the Medical Society of the State of New York, the Association of Military Surgeons of the United States, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1929.

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA

APRIL 4, 1943

A meeting of the Board of Regents of the American College of Physicians was held in Philadelphia at the College Headquarters on April 4, 1943, convening at 10 00 a m , with Dr James E Paullin presiding as President, Mr E R Loveland acting as Secretary and with the following in attendance

James E Paullin	<i>President</i>
Ernest E Irons	<i>President-Elect</i>
Charles H Cocke	<i>First Vice President</i>
Henry R Carstens	<i>Second Vice President</i>
A Comingo Griffith	<i>Third Vice President</i>
William D Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary-General</i>

J Morrison Hutcheson

Walter W Palmer

O H Perry Pepper

T Homer Coffen

Jonathan C Meakins

Francis G Blake

Reginald Fitz

Charles T Stone

William B Breed

Paul W Clough

Edward L Bortz

Acting Editor, ANNALS

*Chairman, Advisory Committee on
Postgraduate Courses and Chair-
man of the Committee on War-Time
Graduate Medical Meetings*

On motion by Dr O H Perry Pepper, seconded and regularly carried, it was

RESOLVED, that inasmuch as the Minutes of the preceding meeting of the Board of Regents have just been published in the ANNALS OF INTERNAL MEDICINE their reading shall be dispensed with

PRESIDENT JAMES E PAULLIN This meeting of the Board of Regents under ordinary conditions would occur at the annual meeting of the College, and at this time I would be the retiring President, and the honor and duties of the office would be assumed by most worthy successor, Dr Ernest E Irons Because of conditions existing on account of the war, at the December meeting of the Board of Regents it was determined to abandon, for the time being at any rate, our annual meeting and all officers were requested to remain in their present status I assure you that I profoundly appreciate the responsibilities and the obligations which have been placed upon me to carry on for another year as your President These duties have been lightened because of the unselfish cooperation of Dr Ernest E Irons, the President-Elect who has willingly given of his time and his talents in helping to further the interests and the activities of the College The Board of Regents and the Board of Governors have been most helpful and the services of Mr E R Loveland Mr Hugland and of Miss Ott have made the duties falling upon me as light as possible To all I am most grateful for your hearty cooperation

Since the meeting of the Board of Regents in December I feel that the officials and the members should be informed of the activities of the College The post-

graduate courses, which were planned and authorized for this year, have been carried out. The last course begins on April 5 under Dr. Chester Keefer in Boston. In the beginning some doubt was expressed as to whether the College was acting wisely in continuing these courses. The results of such activity, up to the present time, have been most gratifying. Every course has been oversubscribed and it is probable that if more had been arranged they could have easily been filled. For example, the course of Dr. Chester Keefer, although it does not begin until April 5, was oversubscribed in February, and it has been enlarged to accommodate eighty applicants instead of the original sixty. Other courses held in Rochester and Minneapolis have been equally as successful. Under conditions such as exist at the present time this experience should serve as an excellent example of the interest of the College and others in postgraduate medical training. It is believed that this type of instruction should be continued if possible during 1944.

Since the annual meeting of the College has been postponed, the Board of Regents recommended that Regional Meetings be held in different parts of the United States. So far Regional Meetings have been held in Philadelphia, Chicago and Boston. Other meetings are scheduled for New Orleans, Washington, Great Falls, Kansas City, Columbus and Jacksonville. It has been my pleasure to attend three of these meetings. The attendance has been all that could be expected. The interest of the members of the College, of the military, naval and civilian practitioners, has been quite gratifying. The type of papers presented and the enthusiasm of the authors in presenting their subjects have been most unusual. The meetings have been a great success and have served a very valuable purpose in advancing the ideals of the College towards the better training of our members in the practice of Internal Medicine. It is my belief that this one feature alone is a great contribution towards the advancement of medical education and to the furtherance of the ideals of practice in Internal Medicine.

A Committee has been appointed by the three medical organizations interested in graduate education to further the distribution of medical instruction on a much wider and a much more comprehensive basis than that which was contemplated originally by the American College of Physicians in its Regional Meetings. A resolution by Dr. Fitz gave your President authority to cooperate with other interested groups and to appoint a committee to further this purpose. It was believed that the American College of Physicians, in cooperation with the American College of Surgeons and the American Medical Association, could direct general courses of postgraduate instruction which could be offered through the Surgeons General of the Army, the Navy, and the Public Health Service to various military installations throughout the country, and to civilian physicians. This purpose has been accomplished. The American Medical Association appointed Dr. Edward L. Bortz, a member of its Council on Scientific Assembly, the American College of Surgeons appointed Dr. Alfred L. Blalock, Professor of Surgery at the Johns Hopkins Medical School, and the American College of Physicians appointed Dr. William B. Breed, Chairman of the Board of Governors, as a Central Committee to direct these activities.

For the first time, so far as I am aware, American Medicine, as represented by the American Medical Association, the American College of Physicians, and the American College of Surgeons, is attempting to formulate a program of graduate medical instruction to be given in various regions of this country. The combined effective strength of all three organizations is thrown into this undertaking with a realization that American Medicine owes an obligation to the physicians of the military forces and to civilian doctors who will not be able, because of increased local demands, to attend local meetings of either one of these associations, to have the benefit of this type of instruction. It is believed that this is a definite step in the advancement of scientific medicine and it is to be hoped that through such cordial,

sympathetic relationships that have been established between these organizations, a program which is just now beginning to be formulated will continue in its great usefulness, not only during the period of the present emergency but perhaps it will make its usefulness known to such an extent that it will be continued hereafter

The Executive Committee of the College appointed a Committee on Planning for War and Post-War Medical Services. This Committee consisted of Dr Walter W Palmer, Chairman, Dr William B Breed, Dr Edward L Bortz, Dr Ernest E Irons and Dr George Morris Piersol, with your President as ex-officio member. A similar Committee appointed by the American College of Surgeons consisted of Dr Irvin Abell as Chairman, Dr Everts A Graham, Dr Frederick Collier, Dr Arthur Allen and Dr James Mason as members. These Committees will act in a consultative and advisory capacity on medicine, surgery and other topics, with a Central Committee nominated by the Board of Trustees of the American Medical Association, consisting of Dr Roger I Lee, Chairman, Dr Fred W Rankin, Dr Harrison H Shoulders and Dr James E Paullin. Perhaps other members will be added to the latter committee.

The Committee on War and Post-War Medical Services, after completing its organization and establishing its various subcommittees in the branches of medicine, surgery and allied specialties, will be composed of men who represent the outstanding thought of the professions in the United States. It will be able to formulate a plan and assume its responsibility in providing sound advice and leadership to any group of individuals who have the real interest of the world at heart in any post-war medical effort that must of necessity be made by the people of the United States after peace is declared. There are many problems which must be considered by this Committee because of our extensive commitments. We must at all times be mindful of the great sacrifice which every physician is making who enters the armed service. This sacrifice is made not only by doctors but by other individuals who volunteer for service. In planning, however, for physicians during the war effort, it is necessary that the newest and latest knowledge of diagnosis and treatment be immediately transmitted to our men in the military services. We should bear in mind that during the present war and after a declaration of peace it will be necessary for many physicians who have served either in tactical units, or in the theater of operations, to have refresher courses in medicine and surgery before returning to general practice. Such should be a privilege extended these men by our government.

A Post-War Planning Committee should select as members of its various subcommittees on post-war medical services physicians who will be willing to give of their time and effort and who will be willing to go as emissaries to foreign countries in order to render medical care. Many of our members who are physically disqualified for military duty, and some who are retained in essential capacities, will help in this undertaking. With the end of the war and the return from military service of younger men, many of those who now occupy essential positions and those who are physically disabled, but capable of active work, can volunteer for this type of non-military service, thus allowing their places to be filled in teaching and other civilian needs by men recently returned from military duty.

The College of Physicians, with other medical groups participated in sponsoring a conference held in New York in March under the auspices of the Finlay Institute of the Americas. It is believed that our sponsoring of this activity was of considerable benefit to the members of our organization and it is hoped that as a result of this conference a sufficient amount of interest was aroused among medical men to go forward with the completion of a program to render this particular type of service.

It is believed that such activities of the American College of Physicians are a distinct part of our obligations to American Medicine and we desire to continue to be of the utmost service to our country and to the military forces in the present emergency.

PRESIDENT PAULLIN The Secretary will kindly present the communications

SECRETARY LOVELAND I have received letters from Drs Barr, Webb, Churchill, Tenney, Lee and Morgan, expressing their disappointment at not being able to be present at this meeting and sending their greetings to the Board I have another communication to the Regents from Acting Governor J Edwin Wood of Virginia, who recommends that the Regents provide a clearer statement of the qualifications for Associateship

(Reads letter from Dr Wood)

The Credentials Committee will probably report on recommendations later in this meeting I have another communication from Governor Edward L Bortz, suggesting a plan by which the Governors shall follow up all Associates in an effort to see that each Associate shall do the necessary work to qualify for Fellowship

(Reads letter from Dr Bortz)

PRESIDENT PAULLIN Gentlemen, you have heard the communication from Dr Bortz What is your pleasure? Would you like it referred to the Chairman of the Committee on Credentials?

DR PALMER I hope the Regents will consider it I happen to be one of those individuals who is opposed to regimentation and I think that if the suggestion is put in a different manner—as an opportunity rather than as a “must,” I would be more in favor of it There are men associated with teaching centers where their opportunities for advancement in their field is far greater than would be obtained by attending a graduate course organized by the College

DR IRONS I think it a fine idea to have Governors given an additional opportunity to father the younger men I don't think there should be any “must,” however, but more of an expression of interest and a hope that the educational progress of these young men will continue The American Board says, “Here is something you should do if you want to do a good job”

DR BREED What attitude should the College Governor take toward recruiting new members in his State? Formerly I took the attitude that it was unwise to proselytize for the College and that we would probably get better men if, through our activities, we make it attractive to them rather than to seek them out There are other Governors, however, who have a different attitude I am a bit in doubt as to what the proper attitude should be It is an important problem that I think worth discussing

DR COCKE Having been a Governor for a long time, I had an entirely different point of view from Dr Breed In a community of large teaching centers of medicine such an attitude is not only understandable but valuable, because young men by their own initiative and interest are trying to advance, and are aligned with various institutions affording such opportunities But, take such a State as North Carolina, I think it is distinctly the Governor's duty and obligation to know who are the up and coming young men in his State and to try to stimulate their interest in such an organization as the College In our State we were early in organizing Regional Meetings, we encouraged and frequently invited these men as our guests to our Regional Meetings and we attempted to stimulate their interest

SECRETARY LOVELAND In regard to stimulating Associates to qualify for Fellowship, I would remind the Board that every Associate of the College receives each year a questionnaire on which he records what he has accomplished during the year—publications, advancements in appointments, postgraduate courses taken, new society memberships, etc This was initiated by the Board as a plan to show we are interested in following each Associate in his effort to qualify for Fellowship

PRESIDENT PAULLIN Gentlemen, if there is no objection, may this letter from Dr Bortz be referred to the Committee on Educational Policy for consideration, with direction to report back to this Board at its next meeting?

(A motion to refer the letter to the Committee on Educational Policy was made by Dr Piersol, seconded by Dr Griffith, and carried)

PRESIDENT PAULLIN May we have the report of the Secretary-General, Dr George Morris Piersol

DR PIER SOL We herewith report the deaths since the last meeting of this Board of the following fourteen Fellows and two Associates

Fellows

Bonney, Sherman Grant	Denver, Colo	November 19, 1942
Byrnes, Ralph L	Los Angeles, Calif	February 16, 1943
Dennison, Archibald S	Lynn, Mass	January 22, 1943
Elliott, Jabez H	Toronto, Ont , Canada	December 18, 1942
Freeman, Elmer Burkitt	Baltimore, Md	December 23, 1942
Kruse, Fred Herman	San Francisco, Calif	January 14, 1943
Layton, Oliver M	Fond du Lac, Wis	December 27, 1942
Porter, Ernest Boring	Altadena, Calif	November 15, 1942
Rowland, Peter Whitman	Memphis, Tenn	January 10, 1943
Stofer, John William	Gallup, N M	January 16, 1943
Watkins, Fonso Butler	Morganton, N C	March 9, 1943
Wilmer, Harry B	Philadelphia, Pa	January 16, 1943
Woltmann, Harro	Mansfield, Ohio	December 27, 1942
Work, Hubert	Englewood, Colo	December 14, 1942

Associates

Allen, Theophilus Powell	New York, N Y	January 27, 1943
Elward, Joseph Francis	Plains, Pa	February 6, 1943

We also report the following new Life Members since the last meeting of this Board, bringing the grand total to 211, of whom 22 are deceased, leaving a balance of 189

Charles L Hess	Bay City, Mich
Ralph King Hollinshed	Westville, N J
Ranald E Mussey	Troy, N Y
Gabriel B Kramer	Youngstown, Ohio
Elijah Kaplan	New Castle, Pa
Spencer Augustus Folsom	Orlando, Fla
Robert A C Wollenberg	Detroit, Mich
Edgar F Kiser	Indianapolis, Ind
William Corr Service	Colorado Springs, Colo
Harry Gauss	Denver, Colo
Harold E Himwich	Albany, N Y
Willard Boyden Howes	Detroit, Mich
Jesse D Riley	State Sanatorium, Ark
Joseph C Placak, Sr	Cleveland, Ohio
Harold R Roehm	Birmingham, Mich
Charles S Bluemel	Denver, Colo
George E Baker	Casper, Wyo
Samuel A Loewenberg	Philadelphia, Pa
Vernon C Rowland	Cleveland Ohio
Frederick Slyfield	Seattle, Wash
Roy Colonel Mitchell	Mount Airy, N C
John T Murphy	Toledo, Ohio
Harold Orr	Edmonton Alta Canada
V Thomas Austin	Urbana, Ill

We also report that the College membership "as of March 14, 1943" was

Masters	4
Fellows	3,829
Associates	1,127
	<hr/>
Grand Total	4,960

An analysis of the number of members serving in the Armed Forces at this date is as follows

	Fellows	Associates	Total
Army	605	346	951
Navy	261	100	361
U S Public Health Service	34	21	55
	<hr/>	<hr/>	<hr/>
	900	467	1,367

This is 27 55 per cent of the entire College membership Seven members have been reported missing in action or their whereabouts as yet not established

We report the following members delinquent in dues for two or more years and therefore, under the Constitution and By-Laws, subject to being dropped at this time
(Reads list of five names)

PRESIDENT PAULLIN You have heard the report of the Secretary-General May I particularly call your attention to the names of two deceased Fellows who in the past had an eminent part in the activities of the College, namely, Dr Jabez Elliott, Toronto, who was a former Vice President and a former Governor of the College, and Dr Harry B Wilmer, Philadelphia, who has occupied various posts in the College and was at the time of his death a member of the House Committee

SECRETARY LOVELAND I should like to suggest a period of thirty days' grace for the entire list of delinquent members This will give any Regent or Governor a further opportunity to contact these men, and thus to give them a second chance All of them have been communicated with on numerous occasions

(Motion was made and seconded that the four men on the delinquent list be given a thirty-day grace period in which to pay their dues, if not paid at that time, their names will be automatically dropped from the roster Motion was put and carried)

(Motion was made, seconded and carried to accept the report of the Secretary-General as a whole)

PRESIDENT PAULLIN We shall now have reports of committees and matters of new business Dr Ernest E Irons, Chairman, will report from the American Board of Internal Medicine

DR IRONS Mr President, I have no formal report because the annual meeting of the American Board will not be held until the latter part of May or June, probably in Philadelphia Contrary to our expectations, applications for examination have not decreased, but greatly increased At the October examination we had somewhat over three hundred examinees and in February the number was between one hundred and two hundred This shows what a load members of the Board are carrying, and I want to express here my very great appreciation for their unfailing diligence In October we held examinations in twenty-eight cities and in thirty-four camps and station hospitals in this country I think the men in the camps appreciated this co-operation and expression of interest of the Board in their welfare In addition, we have held examinations in Puerto Rico, Honolulu and North Africa We have plans for examinations in Australia and in India The Surgeon General of the Army has offered cooperation in getting the questions distributed to foreign regions through

use of the diplomatic pouch I also wish to commend with pleasure the excellent services of the Acting Secretary of the Board, Dr William A Werrell of Madison, he has carried on exceedingly well in the absence of Dr Middleton

The standards of the Board have been maintained at the level that we had attained before the war and we propose to hold them so There were 25 per cent failures on the last written examination and 25 per cent failures among the remainder on the oral examination Regional oral examinations will be held for this country as soon as we can get final returns from the February examination These regional oral examinations will replace the oral examinations that customarily were given at the annual meetings of the American College of Physicians and the American Medical Association Certain difficulties with regard to the sub-specialties in medicine have been overcome, sources of irritation have been adjusted and we now have a group of cooperating sub-specialty committees

I want to express the Board's very great gratification of the nomination and subsequent election of Dr James J Waring to membership on the Board

(Motion to accept Dr Irons' report was made, seconded and carried)

PRESIDENT PAULLIN Next is a report of the Committee on Fellowships and Awards by Dr Francis G Blake, Chairman

DR BLAKE Dr Rulon W Rawson, one of our research fellows working with Dr Means at the Massachusetts General Hospital, completed that fellowship some months ago and has submitted a very satisfactory report on the studies he has been making, and he will continue in Dr Means' clinic this coming year He states that his work under Dr Means has been most profitable and Dr Means has been most helpful, he expresses his thanks to the Regents and members of the American College of Physicians for granting him this fellowship

There are still two active research fellows at work—Dr Carl G Heller, working under the direction of Dr Myers at the Wayne University College of Medicine, and Dr James Hopper, Jr, working on various methods of measuring blood volume under Dr Peters at Yale University School of Medicine

Dr Hopper has lived up to his recommendations when he came from Dr Kerr in California He will complete his fellowship at the end of August, and Dr Kerr has offered him an appointment as Instructor in Medicine at the University of California on the completion of his fellowship in New Haven

(Motion was made by Dr Stroud, seconded and carried, accepting the above report)

PRESIDENT PAULLIN Dr Piersol will report for the Committee on Credentials

DR PIERSOL A full meeting of the Committee on Credentials was held April 3 and the following action taken

- 1 The Chairman and the Executive Secretary were directed to draw up a clarification of the published requirements for Associateship, especially with regard to fundamental training that will be necessary for an Associate to qualify for certification within the specified time limits,

- 2 The Committee agreed in the case of candidates from Canada to accept in lieu of certification by the American Boards equivalent certification in Canada such as fellowship in the Royal College of Physicians or certification by that College if, as and when such is established on at least an equivalent basis with that in the United States,

- 3 The Committee reviewed the credentials of one hundred candidates for Fellowship and in accordance with the mimeographed lists that have been distributed to the Board recommends the election of seventy-seven of whom three were for direct Fellowship, three were physicians who had previously served a five-year Associate term in good standing but had not completed the requirements at the expiration of their terms and consequently had been dropped and four were

advanced to Fellowship as of December, 1943 Three candidates for direct Fellowship were recommended for election first to Associateship, seventeen candidates were deferred for further credentials and three candidates were rejected altogether,

4 The Committee reviewed the credentials of seventy-four candidates for Associateship, mimeographed list of whom is in your hands Sixty-two were recommended for election, eleven were rejected and one was deferred for further credentials,

5 An analysis of the class of Associates elected on April 3, 1938, whose terms expire at this time, is as follows

Qualified for Fellowship	111
Deceased	2
Resigned	1
Dropped for failure to qualify in maximum term	5
Deferred until after the war because of military service	10
Total	<hr/> 129

Eighty-six per cent of that group have qualified for Fellowship

6 The following five practicing physicians have not qualified within the five-year period and under the By-Laws must now be dropped

(Reads list of names)

7 The following group of ten Service physicians have not qualified for Fellowship, but because they are on active military duty their Associate terms may be extended until after the war

(Reads list of names)

(On motion of Dr Pepper, seconded by Dr Stone and unanimously carried the report and recommendations of the Credentials Committee were accepted and approved, after adoption of each section individually)

The following seventy-three physicians, therefore, were elected to Fellowship as of April 3, 1943

Anderson, James Fleming, Los Angeles, Calif
 Anderson, William Arnold Douglas, St Louis, Mo
 Appelbaum, Emanuel, New York, N Y
 Baker, Wyrth Post, Washington, D C
 Banyai, Andrew Ladislaus, Wauwatosa, Wis
 Barnes, Maurice C, Waco, Tex, (MRC), U S Army
 Barnes, Wayne Clifton, Springfield, Mass
 Beber, Meyer, Omaha, Nebr
 Benjamin, Samuel, Washington, D C
 Bennett, Thomas Wade, Columbia, S C, (MC), U S Naval Reserve
 Bloch, Robert Gustav, Chicago, Ill
 Bloom, Meyer, Johnstown, Pa
 Bohorfoush, Joseph George, Madison, Wis, (MRC), U S Army
 Brandstadt, Wayne Glassburn, (MC), U S Army
 Brewer, Kenneth Arthur, (MC), U S Army
 Bromberg, Leon, St Louis, Mo, (MC), U S Naval Reserve
 Brosnan, James Timothy, Worcester, Mass
 Brumm, Harold J, St Joseph, Mo
 Carey, Lawrence Sherwood, Philadelphia, Pa
 Carl, Louie Tate, Jackson, Miss, (MRC), U S Army
 Coffin, George Jarvis, New York, N Y
 Crager, Jay Cecil, Beaumont, Tex
 Dufault, Paul, Rutland, Mass

Eaton, Hamblen Cowley, Harrisburg, Pa , (MC), U S Naval Reserve
 Edson, Reginald Campbell, West Hartford, Conn
 Elliott, Clarence Kilgore, Lincoln, Nebr
 Farber, Jason Engels, Buffalo, N Y
 Filberbaum, Milton Bayard, Brooklyn, N Y , (MC), U S Naval Reserve
 Flood, Charles Albert, New York, N Y , (MRC), U S Army
 Gilbert, James Thomas, Jr , Bowling Green, Ky , (MRC), U S Army
 Goldberg, Harold Herbert, Newark, N J
 Gregg, Frank John, Pittsburgh, Pa
 Healy, Thomas Charles, Argyle, N Y
 Herring, Albert Crawford, New York, N Y
 Hollingsworth, Merrill Windsor, Santa Ana, Calif
 Hunnicutt, Thomas Nathaniel, Jr , Newport News, Va
 Johnstone, Benjamin Irvine, Detroit, Mich
 Josey, Allen Izard, Columbia, S C , (MRC), U S Army
 Kehl, Kenneth Charles, Racine, Wis
 Keller, William Karl, Louisville, Ky , (MC), U S Naval Reserve
 Kendall, Ralph Emerson, Hartford, Conn
 Levan, John Boyer, Reading, Pa , (MRC), U S Army
 Lundy, Clayton Jackson, Chicago, Ill , (MRC), U S Army
 Markowitz, Benjamin, Bloomington, Ill
 Marks, Jerome Alexander, New York, N Y
 Marty, Frederick Nicholas, Syracuse, N Y
 Mayer, Joseph Ralph, Rochester, N Y
 McCauley, Lewis Ross, Punxsutawney, Pa
 Miller, Malcolm White, Philadelphia, Pa
 Molyneux, Arthur Van Horn, Honolulu, T H
 Muether, Raymond Oliver, St Louis, Mo
 Mufson, Isidor, New York, N Y
 Ormond, Allison Lee, Black Mountain, N C
 Phelps, Maxwell Overlock, Hartford, Conn
 Rutledge, David Ivan, Boston, Mass , (MRC), U S Army
 Salley, Samuel Marion, Miami, Fla , (MRC), U S Army
 Saslow, Benjamin I , Newark, N J
 Schnatz, Frederick Theodore Buffalo, N Y
 Schwedel, John Bernard, New York, N Y , (MC), U S Naval Reserve
 Schweitzer, Harold Theodore, Buffalo, N Y
 Skinner, Norman Stewart, St John, N B , Can
 Soloff, Louis Alexander, Philadelphia, Pa
 Steinberg, Charles LeRoy, Rochester, N Y
 Torbert, Harold Chester, San Diego, Calif
 Traub, David Strouse, Louisville, Ky , (MRC), U S Army
 Tyler, Richard Smith, Cincinnati, Ohio
 Wall, Emmett Daniel, Peoria, Ill , (MRC), U S Army
 Wilkinson, George Richard Greenville, S C
 Williams, Byard, New York N Y
 Williamson, Charles Grant, Brooklyn N Y
 Wilson, Olin Glenwood Canton, Ohio, (MRC), U S Army
 Wilson, Walter John Jr , Detroit, Mich (MRC), U S Army
 Wright, Willis Dean, Omaha, Nebr (MC), U S Naval Reserve

The following four physicians were elected to Fellowship as of December 1943

Hughes, John Davis, Memphis Tenn , (MRC), U S Army
 Jones, Charles Alexander, Philadelphia, Pa , (MC), U S Naval Reserve

Winn, William Alma, Visalia, Calif

Wise, Irvin Milton, Mobile, Ala

The following sixty-five physicians were elected to Associateship as of April 4, 1943

Acosta-Velarde, Antonio, Arecibo, P R

Allen, Glen Ivan, Peoria, Ill , (MRC), U S Army

Allen, Irene Viola, East St John, N B , Can

Bell, George Olaf, Waban, Mass

Berberich, Walter Francis, (MC), U S Navy

Bettison, William Leslie, Grand Rapids, Mich , (MRC), U S Army

Bleecker, Philip Bernard, Memphis, Tenn , (MRC), U S Army

Brink, James Russell, Grand Rapids, Mich , (MC), U S Naval Reserve

Bruckman, Frederick Sweet, San Francisco, Calif , (MRC), U S Army

Buis, Lester James, Richmond, Va

Burns, Frederic Joseph, Providence, R I

Butler, Stuyvesant, Winnetka, Ill

Carlisle, Margil Clinton, Waco, Tex

Carter, Harold Robert, Denver, Colo

Chapman, Asher Spafford, Rochester, Minn

Chisholm, Donald Raymond, Kealia, Kauai, T H

Craddock, George Barksdale, Lynchburg, Va , (MRC), U S Army

DeLaureal, Thomas Hugh, Lake Charles, La

Edger, Herbert Downing, (MC), U S Army

Eigenbrod, Frederick August, New Orleans, La , (MRC), U S Army

Ellinger, George Frederick, Honolulu, T H , U S Public Health Service

Fischl, Arthur Allyn, Long Island City, N Y

Foret, Marcel Jean, New Orleans, La , (MRC), U S Army

Garcia, John Edward, New Orleans, La , (MRC), U S Army

Gill, Charles Chute, (MC), U S Army

Goldman, Bernard Alvin, New Orleans, La , (MRC), U S Army

Gordon, Abraham Maury, New Orleans, La , (MRC), U S Army

Goyette, Edwin Matthew, (MC), U S Army

Hanford, Russell Bratton, Oakesdale, Wash , (MRC), U S Army

Hanlon, Thomas Joseph, St Louis, Mo , (MRC), U S Army

Hedges, Robert Nathaniel, Chicago, Ill

Hoffman, Reuben, Henryton, Md

Hollander, Joseph Lee, Philadelphia, Pa , (MRC), U S Army

Kapernick, John Stuart, Rochester, Minn , (MRC), U S Army

Kaplan, Murrel Herman, New Orleans, La , (MRC), U S Army

Katz, Kermit Harry, Dorchester, Mass

Kramer, Milton Lurie, New York, N Y , (MRC), U S Army

Layne, John Anthony, Great Falls, Mont

Leslie, Alan Noah, New York, N Y , (MC), U S Naval Reserve

Lovell, Harold William, New York, N Y

Mansmann, James Andrew, Pittsburgh, Pa

Marino, Frank Xavier, New Orleans, La

Morris, Harold Thoes, Topeka, Kan

Pedigo, George William, Jr , Louisville, Ky

Pesquera, Gilberto Severiano, Mount McGregor, N Y

Powell, George Merle, (MC), U S Army

Roberts, Charles James, Enid, Okla , (MRC), U S Army

Rogers, Howard Milton, St Petersburg, Fla

Rosenblum, Louis A , Forest Hills, L I , N Y

Rothman, Theodore, Paterson, N J
 Shaffer, Carl Francis, Detroit, Mich
 Shipp, Leland Parmater, Battle Creek, Mich
 Skinner, Robert Barrett, (MC), U S Army
 Smart, Reginald Hughes, Los Angeles, Calif
 Stein, William, New Brunswick, N J, (MRC), U S Army
 Stevens, Joseph Blackburn, Greensboro, N C, (MRC), U S Army
 Strong, Paul Stone, Baltimore, Md, (MRC), U S Army
 Swanson, Paul Richard, Chattanooga, Tenn, (MRC), U S Army
 Thompson, Charles Middleton, Philadelphia, Pa, (MC), U S Naval Reserve
 Ullman, Robert Adolph, Buffalo, N Y
 van Ravenswaay, Arie Cornelius, Boonville, Mo, (MRC), U S Army
 Walsh, Bernard John, Washington, D C
 Whims, Clarence Bernard, Ventnor City, N J, (MRC), U S Army
 White, Major Samuel, (MC), U S Army
 Zimmerman, Solomon Lincoln, Columbia, S C

(Dr Charles H Cocke, First Vice President, takes the Chair)

DR PAULLIN In the absence of Dr Lee, I was asked to make a report for the Committee on Public Relations

The Committee on Public Relations of the College met at the College Headquarters at 3 00 p m, Saturday, April 3, 1943, with the following members present Dr A C Griffith, Dr J Morrison Hutcheson and Dr James E Paullin, Acting Chairman Drs Roger I Lee and David P Barr were unable to be present

The Committee recommends

(1) That the resignation of Dr E J Engberg, F A C P, Faribault, Minn, be accepted,

(2) It is recommended that the dues of — — — — —, F A C P, be waived for the years 1942 and 1943 due to illness, and that his check be returned

It is recommended that the Secretary transmit to him the best wishes of the Board of Regents for a speedy recovery

(3) The communication of Dr C O Bailey, F A C P, Los Angeles, Calif, concerning the establishment of an American Board of Medical Educators for the purpose of improving the teaching of medical subjects in medical colleges be referred to the Association of American Medical Colleges, without recommendation from this Committee It is the belief of the Committee on Public Relations that matters relating to medical teaching are more of a problem of the Association of American Medical Colleges than that of the American College of Physicians

Respectfully submitted,

Dr A C GRIFFITH

Dr J MORRISON HUTCHESON

Dr JAMES E PAULLIN, Acting Chairman

(The above report was accepted section by section and by motion, made, seconded and carried, the report as a whole was approved)

(Dr Paullin resumes the Chair)

PRESIDENT PAULLIN The next item on the agenda is the report of the Advisory Committee on Postgraduate Courses by Dr Edward L Bortz, Chairman

DR BORTZ Mr President, under the auspices of the College three courses in Internal Medicine have been offered this past winter The first course was at the University of Minnesota, January 25-30, in which the published maximum registration was 50, but in which 77 men were accommodated Of these 32 were Fellows of the College, 17 Associates and 28 non-members Nine of the registrants were from the military Services

The second course was given at the Mayo Clinic under Dr. E. H. Ryneerson, February 1-6, in which the maximum published facilities were 50, but in which 58 were finally accommodated. Of this group 32 were Fellows, 16 Associates and 10 non-members. Nine of the registrants were from the military Services.

The third course, under Dr. Chester S. Keefer at Boston University, April 5-10, had published maximum facilities for 50, but accommodations have been provided for a total of 82. Of these 38 are Fellows of the College, 20 Associates and 24 non-members. 26 registrants are from the military Services.

The College, through these courses, has created opportunity for serious graduate study for 217 doctors. We staggered these courses so that members could take more than one course if desired. Several members took advantage of this opportunity and two members registered for all three courses. It is the thought of the Committee that in the future we shall follow the staggering system, making these facilities available to all members. What the future holds for these courses, of course no one can say, but there appears to be a very healthy interest among a considerable number of men, among members of the College and also among physicians who are looking forward to membership in the future.

The Committee recommends that certain courses be offered next autumn, including a course in Allergy of one week's duration at the Massachusetts General Hospital under Dr. Francis Rackemann, a course in Diseases of the Endocrine System of one week's duration, in Chicago, under Dr. Willard Thompson, a course in Special Medicine, two weeks' duration, in Philadelphia, with subjects divided somewhat along the following lines:

- One day's instruction in Neuropsychiatry
- One day's instruction in Cardiovascular Problems
- One day's instruction in Gastrointestinal Disorders
- One day's instruction in Problems of Cancer
- One day's instruction in Metabolism
- One day's instruction in Treatment of Shock, Plasma and the Protein Fractions of Blood, etc.,

a course in General Medicine, one week's duration, at the University of Michigan under Dr. Cyrus Sturgis, and possibly a course in General Medicine of one week's duration, in San Francisco, although this latter suggestion will require further consideration and investigation.

(A motion to accept the above report was made by Dr. Stone, seconded and carried.)

DR. PEPPER: What is the explanation, Dr. Bortz, of these large numbers of men taking the courses, considering present existing conditions of shortages of doctors and overwork of doctors? What are these men doing and how do they get away?

DR. BORTZ: We were surprised to find so large a registration. Many of them are in the Armed Forces already. Others perhaps take advantage of these courses to get a brief vacation from practice. I do not know anything more.

PRESIDENT PAULLIN: Dr. Irons will now give a report of the Committee on Educational Policy.

DR. IRONS: We met with Dr. Bortz' Committee on Postgraduate Courses yesterday, and Dr. Bortz has already covered the activities quite thoroughly. The Committee on Educational Policy has been concerned with the organization of this joint activity of American medicine, The War-Time Graduate Medical Meetings, also in the program President Paullin outlined at the beginning of this meeting concerning the activities of the College along with other organizations in preparing for post-war opportunities for physicians returning from the Service. This Committee is actively interested in the entire program and is in agreement with the matters that have been proposed.

(Motion to accept report of the Committee on Educational Policy was made by Dr Pepper, seconded by Dr Palmer and carried)

PRESIDENT PAULLIN Next is the report of the Chairman of the Board of Governors, Dr William B Breed

DR BREED Mr Chairman, members of the Board of Regents It is quite obvious that I can give you no definite report from the Board of Governors because that Board has not met since your last meeting, nor have I as yet functioned as Chairman of the Board because there has been no meeting since my election to office However, as I have previously reported, I have communicated by mail with all of the Governors, urging them to organize Regional Meetings I have had a large percentage of replies, some enthusiastic and some cautious, but there has developed considerable action as you have heard from President Paullin

Since last October there have been three Regional Meetings—in Philadelphia, Chicago and Boston—all highly successful, and between now and next September seven additional Regional Meetings are scheduled—New Orleans, Washington, Great Falls, Kansas City, Columbus, Jacksonville and New York The suggestion of the Board of Regents that Regional Meetings be stimulated has borne fruit

In relation to the participation of Governors in the activities of the College, you might be interested in learning how many of our Governors are involved in the work of the Committee for War-Time Graduate Medical Meetings, which has been established and which is going through the process of organization We shall have a group of twenty-four consultants in various categories of specialization, and on this Board of Consultants twelve Fellows from the American College of Physicians have been appointed Among the Regional Committees, of which there are twenty-four, there are thirty-one Fellows of the College of Physicians as members Of the Regional Committeemen, fourteen of the appointees from the American College of Physicians are Governors, from the Board of Regents, there are three on the Regional Committees The activities of the Governors from now on must necessarily be confined or developed in the field of Regional Meetings and membership on the Committee on War-Time Graduate Medical Meetings

(On motion of Dr Griffith, seconded by Dr Palmer and carried, the report of the Chairman of the Board of Governors was accepted)

DR GRIFFITH In arranging our Regional Meeting for Kansas City, I invited the Governors of all participating States to come to Kansas City for a preliminary organization meeting They all responded and we had an all-day session It is a suggestion for future Regional Meetings that participating Governors be called into conference to create a better feeling and to impress them with the fact that they are making a contribution

PRESIDENT PAULLIN This is a wise suggestion May we have the report of the Committee on ANNALS OF INTERNAL MEDICINE by Dr Walter Palmer, Chairman

DR PALMER The Committee on the ANNALS met at the College Headquarters at 4 00 o'clock yesterday Dr Barr was excused The following matters were discussed and presented for your information and approval

1 Mr Loveland informed the Committee that our printers, the Lancaster Press, would have to increase the cost of printing the ANNALS, due to increased wages and other difficulties due to the war, from \$1,000 00 to \$1 100 00 above the present contract The Lancaster Press suggested it would absorb the increase in cost up to July 1 if the College would authorize an increase at that time This would mean that the College would have to look forward to an increase of \$600 00 to \$700 00 for the balance of the year and a further increase in 1944 The Committee recommends this increase be authorized

(Motion to adopt this section of the report was made by Dr Palmer, seconded by Dr Griffith and carried)

I should call attention to the fact that Mr Loveland reports that Government regulations require that there be 10 per cent reduction in paper for 1943, but I understand that that will leave ample paper to publish in the ANNALS what we have planned We shall hear from Acting Editor Clough later

2 The Committee has encouraged Dr Clough to publish a series of medico-legal papers sponsored by Dr Hubert W Smith of the Harvard Law School This series will appear in the April issue

3 The Committee recommends the granting of the request of a review journal in Buenos Aires the privilege of reviewing articles appearing in the ANNALS This review journal is sponsored by reputable men as far as we know, not only in Buenos Aires but in several of the South American countries It seemed to us that the request is quite in order and we would like approval of that recommendation

(Motion to accept this section of the report was made by Dr Stroud, seconded and carried)

In closing this report, I would like to say that the Committee believes the College is particularly fortunate in having Dr Clough to act as Editor in the absence of Dr Pincoffs

(Motion to accept the above report as a whole was made by Dr Griffith, seconded by Dr Coffen and carried)

PRESIDENT PAULLIN May we hear now from the Editor of the ANNALS, Dr Clough

DR CLOUGH I have only a few points to present for information As far as material is concerned, we still have a fair supply We have accepted for publication for July and future numbers seventy main articles and about fifty case reports It would require a year to publish these case reports and the main articles would run for eight or nine months As Dr Palmer has reported, we shall have to cut down on the amount of paper we use, but assuming that this reduction is not taken care of by diminished circulation, it will mean only a relatively minor diminution in the size of the journal It would still give us two hundred pages per number, one hundred fifty of which would be scientific material and fifty would be reserved for College News Notes, advertising and miscellaneous material I think that will be quite adequate

We contemplate devoting the June number entirely to the publication of papers presented at Regional Meetings or Postgraduate Nights For the most part, these papers present relatively little in the way of new investigation, but many of them are excellent reviews and we felt justified in using one number of the ANNALS to bring out such material for its educational value

The April number will be devoted to medico-legal articles Many of these articles will be of general interest, some of them not so much of general interest, but on the whole they are a good series of articles

One matter I referred to the Committee and Dr Palmer has asked me to bring it up here for action It is mainly to place the responsibility upon the Regents When Dr Smith approached me concerning these legal articles, he intimated some editorial compensation would be welcome Such action has not been customary in the past

PRESIDENT PAULLIN Before a motion is made, may we hear from Mr Loveland about the circulation of the ANNALS

SECRETARY LOVELAND I predicted at the last meeting of the Board of Regents that we might have a definite shrinkage in circulation, but said that we would make an extra effort to promote circulation among non-members, also to increase our advertising volume in order to keep up the income With 1370-odd members in the Armed Forces with waiver of dues, the circulation naturally would be greatly curtailed However, I am pleased to report that there has been a surprising number of Service doctors who have waiver of dues but who desire to continue receiving the ANNALS

and have subscribed to it at the cost price Furthermore, the offices of the Surgeons General have sent in numerous subscriptions for the large Army and Navy hospitals, with the result that the circulation is keeping up very well A year ago, the March circulation was 5,822 copies, whereas the March circulation for this year was 5,750 copies

With regard to the advertising, there has been a slight shrinkage—possibly one and a fraction pages per issue

PRESIDENT PAULLIN You have heard the supplementary report by Mr Loveland The report of Dr Clough is before you for consideration

(Motion that no honorarium be granted for the medico-legal material for the April issue was made, seconded and carried)

PRESIDENT PAULLIN Next is the report of the Treasurer, Dr William D Stroud

DR STROUD The Auditor's Report and the Statements of Operation for 1942 reveal that there was a balance to surplus of \$27,988 83, somewhat in excess of any previous year since 1938 The total Funds of the College, as of December 31, 1942, were

Endowment Fund	\$136,329 06
General Fund	190,569 76
	<hr/>
	<u>\$326,898 82</u>

The College has invested at book value, as of March 31, 1943, \$252,536 68, the cash value at this date of which was \$254,430 00, or an appreciation of \$1,893 32

A condensation of the Statements of Operation will be published in an early issue of the ANNALS

(Motion to accept the Treasurer's report was made by Dr Griffith, seconded and carried)

PRESIDENT PAULLIN Next is the report of the Committee on Finance by Dr O H Perry Pepper, Chairman

DR PEPPER The Finance Committee of the American College of Physicians met at the College Headquarters on April 3, 1943, with Drs Charles T Stone and O H Perry Pepper of the Committee, Dr William D Stroud, Treasurer, and Mr E R Loveland, Executive Secretary, present Dr James D Bruce was not present

The Committee begs to report the following items

1 In 1942 there was added to the

Endowment Fund	\$ 3,742 68
General Fund	24,246 15
	<hr/>
Total	<u>\$27,988 83</u>

This is better than was expected

2 The Budgets for 1943, as adopted at the December, 1942, meeting of the Board of Regents showed

Anticipated Income	\$82 410 00
Anticipated Expenditures	78 065 00
	<hr/>
Anticipated Balance	<u>\$ 4 345 00</u>

There has developed nothing which changes these estimates except in two items

3 At the December meeting, the Regents appropriated \$2 500 00 for Regional Meetings, it being estimated that ten meetings at \$250 00 each would be adequate

The Executive Secretary now reports that two items have been higher than expected

- a Printing of programs in a number sufficient to distribute to all Army and Navy Officers in the district,
- b Traveling Expenses

The Finance Committee therefore recommends an additional appropriation of \$1,000 00 for this purpose

4 Since the Budgets were approved, an increase in wages to printers has raised the cost of production of the ANNALS

The Finance Committee therefore recommends that an additional \$1,000 00 be appropriated to the ANNALS, this being the amount requested by the Committee on the ANNALS OF INTERNAL MEDICINE

5 There is now in the Endowment Fund cash equalling \$5,195 99 Drexel & Co recommends the purchase of 5 U S War Bonds, Series "G," paying 2½% The Endowment Fund already holds \$76,400 00 of Government Bonds and no common stock

The Finance Committee voted to request Drexel & Co to consider the investing of this sum in common stock

6 The Finance Committee reports that the College has established its status as non-resident tax free in Canada with regard to securities, and has had refunded to it \$55 00, representing 15% tax imposed on past dividends on the International Nickel Co of Canada stock

7 The Finance Committee is satisfied with the financial status of the College and begs to point out that if the two appropriations recommended in the report are made, it will have an anticipated balance for 1943 of \$2,345 00

(Motion to accept the report of the Committee on Finance was made by several, seconded by Dr Cocke and carried)

PRESIDENT PAULLIN We need to appoint a successor to Dr Harry B Wilmer, deceased, to the House Committee The present members consist of Drs William D Stroud and T Grier Miller

DR PEPPER I nominate Dr Charles Brown, Professor of Medicine at Temple University

(The nomination was seconded and carried)

PRESIDENT PAULLIN Next I have a letter addressed to me, being a resignation from Dr O H Perry Pepper as Regent of the College

(Dr Pepper leaves the meeting)

(Dr Paullin reads letter)

Gentlemen, if you would permit the Chair to make a few comments, I think Dr Pepper's action can be applied to all of us, who have been asked to continue to serve in one capacity or another Personally, I feel very deeply that at this particular time the College has an opportunity of accomplishing one of the greatest jobs that it ever will be permitted to do again, and it is through the advice and counsel and work of such men as Dr Pepper and other members of the Board of Regents that we are going to be able to accomplish that purpose I do hope that the Board will not accept this resignation

(Motion not to accept the resignation of Dr Pepper was made by Dr Cocke, seconded by Dr Griffith and unanimously carried)

(A messenger asked Dr Pepper to return to the meeting)

PRESIDENT PAULLIN Dr Pepper, I am directed by the Board of Regents to inform you, Sir, that under no circumstances would they consider accepting your resignation

DR PEPPER I appreciate that, but I wanted to give a chance to some of the men

serving the College, not yet recognized, to be placed on the Board of Regents, but I assure you I shall continue to do what I can

PRESIDENT PAULLIN Gentlemen, the next item, I think, is one of the greatest of interest to the College It has to do with the matter that I briefly referred to in my opening remarks, to war and post-war planning of the College Dr Bortz, would you like to discuss the Regional Meetings together with the present method that you have established, namely, the War-Time Graduate Medical Meetings, with Dr Breed and Dr Blalock, or would you like to take up the matter as a whole?

DR BORTZ Mr Chairman, the Regional Meetings of the College during the past few years have been increasingly successful as disclosed by the interest and attendance on the part of members When war clouds began to gather and it became evident that our Nation was going to become involved, the leaders in American medicine wanted to play a just rôle and take their responsibility in providing the medical supervision that was imminent in the action to come In certain sections of the country overtures were made to commanding officers of military installations to the end that the College might put on a series of courses of instruction in their hospitals Here in Philadelphia we contacted the commanding officer of the Naval Hospital and asked him whether the staff of the hospital would be interested in having the American College of Physicians put on a series of graduate nights He discussed the matter with the staff and it was enthusiastic about such a proposition That was more than a year and a half ago We have in Philadelphia a splendid group of teachers who was very glad to go to the Naval Hospital and conduct this series of Postgraduate Nights All members of the hospital staff attended, and they were so pleased with the course that they immediately asked that another be given as soon as possible A similar activity was developed in the Chicago area and the same experience was had there Now, wherever the College has taken the leadership in putting on these courses they have been substantially successful

The College Regional Meetings, let me point out, are at present being held in the metropolitan areas, for example, in Washington, in New Orleans, in Kansas City, in Columbus and elsewhere—in each area there is already a concentration of expert medical talent

It seemed to the officers of our College, to the American Medical Association and to the American College of Surgeons that a movement in the direction of the military installations away from the metropolitan areas is needed There is a greater need for teaching in the medical installations away from these centers and that, in essence, was the motivating idea behind the creation of the Committee appointed by Drs Paullin, Abell and Rankin to instrument these War-Time Graduate Medical Meetings

For purposes of organization and action, the country has been divided into 24 different areas and for each of these areas there is a working committee of 3 doctors, one to represent the American College of Physicians, one the American Medical Association and one the American College of Surgeons

In addition, about ten days ago in New York City, Drs Paullin, Abell and Rankin appointed a group of 23 national consultants, a Board to act in a consulting capacity for the purpose of selecting men to go into the military installations for purposes of teaching Also, each of these consultants is asked to draw up a key program that may be used wherever these programs are conducted at military installations

Before the personnel of the Board of National Consultants was selected a far-reaching study of the various men in the various special fields was made by the directing heads of the three organizations, and these organizations then selected the following men to make up the Board of National Consultants, all of whom have a national reputation, widespread contacts, years of experience in various special fields and who have the ability to procure the services of the other men who will be called upon to cooperate in this program

(Dr Bortz read list of Consultants)

The list of the men on the Regional Committees is too long to read, but we have an outstanding group of men who will act on the various Committees throughout the entire Nation

We shall send a copy of the preliminary announcement to all members of the Board of Regents and to the officials of the three participating organizations. The program, in brief, is an endeavor to carry into the camps away from the metropolitan areas a group of top-flight teachers to conduct teaching ward rounds, clinical pathological demonstrations or to use motion pictures, for instance, in the venereal disease field. They may conduct conferences, seminars or anything that the commanding officer and the teachers desire. Visualize, if you will, a group of six hospitals in an area like eastern Pennsylvania. One day we shall send a team of two or possibly three men to conduct teaching rounds, one day from 10 00 to 12 00 in the morning and from 2 00 to 4 00 in the afternoon. They may use movies and have question and answer periods. From 7 00 to 9 00 in the evening they may conduct another question and answer period or give a lecture. Monday of the next week they may go to another hospital and the following Monday to still another hospital in the area, and so on until they have made the rounds of the four or five installations assigned to them.

On Tuesday of each of the weeks a second team in another field will conduct programs, moving along each week from one installation to the next and so on through the week. In that way no individual will be asked to give more than one day a week for a series of four, five or six weeks, approximately twice a year, to this teaching program.

The movement is a worth while one if we can judge from the enthusiasm that has been voiced on the part of practically every individual with whom it has been discussed. However, last evening an adverse comment was voiced by one of the men who is acting as a National Consultant who expressed doubt whether men of the caliber desired would have time and could be persuaded to join in this movement, but let me point out this fact to you, gentlemen, that already this particular teacher is heavily engaged in a teaching program. He is already going from camp to camp. Other highly competent men have been recklessly generous with their time in visiting hospitals away from the metropolitan areas. This movement is merely an attempt to systematize and make more effective the magnificent work they are already doing.

We have three of our national organizations behind this movement, the American Medical Association, the American College of Physicians and the American College of Surgeons. Although there has been no publicity as yet, other societies have written in and requested that their names be attached to the group of sponsors.

When Dr. Byrl Kirklin was selected as one of the National Consultants he said he would immediately start to organize the radiologists of the country, ready to go anywhere the Committee wishes to send them. A similar opinion was voiced by Dr. Edward Strecker of the American Psychiatric Association and by Dr. Ralph Pemberton of the American Rheumatism Association. Dr. Pemberton said this movement is one of the most significant developments in teaching of medicine today, that it is a great opportunity and he considers it a real privilege to participate.

It appears that there is a place for such a movement and that there will be an adequate number of qualified teachers who will be willing to suffer the inconvenience of going to these military installations to instruct these younger doctors. In this way they will be playing a very real rôle in the war effort, a rôle that has been denied to a good many of our teachers because they are over-age or have some slight physical limitation or because they are regarded essential on teaching faculties.

Some time ago in Chicago Dr. Irons and I visited the offices of the Council on Medical Education and Hospitals of the American Medical Association and Dr. Weiskotten has written to the deans of the medical schools throughout the country concerning this project. We are just beginning to get reports from the deans, and

they are eager to place their faculties as far as possible at the command of this Committee for the purpose of organizing the personnel for giving these courses

We expect to have a teaching medical faculty on a national scale, a great pool of the finest medical talent that the country has to offer, under the supervision of nationally known consultants in the special fields, implemented through well-chosen representatives acting as local committees in the twenty-four different areas. We believe we have a new instrument here, created for the purpose of mobilizing the teachers of medicine in this country to help the medical men of the Armed Forces in a most effective manner.

A number of teachers have expressed the opinion that this activity will be of equal importance with that of the instruction of undergraduates in the medical school.

I may say that the three Surgeons General have been kept informed about the activities all along the line and as soon as any new development comes along, information is sent them. We anticipate that the Surgeons General will draw the attention of their various commanding officers in Army and Navy hospitals to these programs. In that way we believe a prompt and enthusiastic response will be obtained.

PRESIDENT PAULLIN: May we also hear from Dr. Breed who is the representative on that Committee of the American College of Physicians?

DR. BREED: I have nothing specific to add.

DR. IRONS: This is a great opportunity for American medicine, it offers an opportunity to take the lead in this war-time activity and also for American medicine to work as a whole in questions which are bound to come in the post-war period. American medicine must take a more active and positive part in making plans for the post-war world. Things will be different than they were before the war. We might just as well recognize that. In those changes that are bound to come we must see to it that American medicine has its part in directing the kind of medical service that people are going to get. Here is our opportunity.

Mr. Chairman, I should like to hear from Brigadier Meakins.

BRIGADIER MEAKINS: Mr. President, we are faced in Canada with very much the same problems as you. Much of my present work evolved through my insistence there be plans for looking after the men in the Armed Services in the way of intellectual and professional instruction. Particularly do I fear the result of the acceleration of the undergraduate medical program and the curtailment of his opportunities, as they existed in peace time, for two to five years of postgraduate experience and practice under his superiors.

Some of the problems in our country are a little worse than yours. Our Army and Navy and Air Force are not comparable in size by any means. Many of our medical officers are scattered throughout the country in camps far removed from metropolitan areas. It is a great problem to keep up their professional morale. We are proceeding along three lines. We have appointed a corps of eight consultants whose duty it is to be on the road constantly, visiting each station, making rounds, discussing the problems, operating if necessary, introducing new methods of procedure and bringing aid to these men who have been in service over three years, who never have an opportunity to get back except on two weeks' annual leave which should not be devoted to professional work. Many of these professional men at camps do not see the sick. The sick in the Army should be a minimum. It is the medical officer's job to see that the soldiers do not get sick. This is quite a reversal of the usual concept of the practice of medicine. The usual concept of the majority of our profession is not to pay very much attention to the individual as long as he is not a patient.

We were late in establishing a Procurement and Assignment Board. The name is exactly the same as yours and was copied. After a few months of its operation it was found that it was not the scarcity of doctors that made the civilian hardships but the maldistribution of doctors, and that was due to a variety of causes. Dentists were badly distributed, faculties of medical schools were badly depleted, nursing service

was being disrupted. Many could not get a nurse although there were plenty of nurses had they been properly distributed.

The Procurement and Assignment Board, through the Minister of National Defense and the Privy Council, was instructed to make a survey of all the medical and health requirements of the Dominion. There were very wide terms of reference, and not only will it cover the Armed Forces but also hospitals and their requirements, medical schools and their requirements, departments of health, provincial and federal. It will cover the nursing service, the dental service, the distribution of medical manpower in villages, towns and cities, in fact, all social agencies that pertain in any way to health.

You may have seen in the press a note that was laid on the table of the House of Commons, called the March Report, which is analogous but by no means identical to the Beveridge Report. The March Report contained a great deal of suggested legislation or suggested ideas for legislation which will undoubtedly bring to the fore very strongly health insurance and the provision of a first-class medical service and health service to the people, so far as it is possible for our country to give them.

We have inherent in our method of government what we call "Provincial rights," what you call "State rights." These rights are very jealously maintained and no matter how paternal and generous the federal government may be, each of the provinces has to be dealt with separately. That leads to complications when one is dealing with health problems, because health and disease are no respecters of rivers or artificial boundaries.

The question of post-war education for the medical profession has been agreed to. Any man who has had his usual course of education interrupted, including his postgraduate education in hospitals, shall have one full year's graduate education in medicine or any of its specialties at the expense of the federal government. This is as generous as we can afford. He will be given an adequate amount, I think about One Thousand Dollars a year, as allowance.

We are now trying to organize the hospitals so that they will have a plan ready when demobilization begins, the hospitals to take these men on as an increased number of residents, I think there will be a time when we will swing back to the regular course of medical study, that we shall then need these extra men even more than now. To find places for fifteen hundred to two thousand such young men will be a difficult job. We want to give them actual graduate study, not lip service. We are not now producing specialists. True, we are producing a few psychiatrists, but for the most part specialists now are not being trained. At the end of the war surgeons will be of the rough and ready kind of the front lines and what they have been able to learn in our military, naval and air force hospitals. You can talk at a person all you like, but it is the doing—good medicine and good surgery under supervision—that's the best way to train good men. Our local societies and our universities will each attempt this year to hold at least one, if not two, of what we may call post-graduate weeks, Monday through Friday, five days. Because we are so scattered, it is difficult to bring any volume of men together. We are hoping to stagger these meetings so as to send experienced men to take the places of those on leave to take these courses. The movement of men overseas also interferes, because their sudden movement as reinforcements may make them miss such opportunities. I am seeking to have such men, when they are warned for overseas duty, to be sent at Government expense, on pay and allowances, to take the next course available so that they shall not lose out altogether.

Mr. Chairman, it is very refreshing for me to hear what you are doing. It is helpful because we have the same problems and it is advantageous to see how other people are solving them.

DR. BREED. In the earlier days of the war, the Surgeon General allowed eighteen months between the time of graduation and induction into the Service of doctors, in

order to allow them a year's internship. Now they have changed that and reduced the number of months to twelve. It is obviously impossible to accommodate all of these boys with a twelve month internship when only twelve months are allowed between graduation and time of induction, and it seems to me that the Surgeon General's Office must change that back to eighteen months or the hospitals will have to contract their term of internship to nine months.

PRESIDENT PAULLIN For your information, through the Committee on Allocation of the Procurement and Assignment Agency, in cooperation with the War Participating Committee of the American Medical Association, representations have been forcibly made to the Surgeon General and to the Secretary of War concerning the situation Dr. Breed has just outlined. The present status is: There will be no reduction in the time between graduation and induction. Men will have to begin their internships immediately after graduation at Government hospitals. If a man does not complete his one year of rotating internship, which they much prefer, or his one year in medicine, he will be given an opportunity under the present set-up to finish his three extra months in some hospital approved for internship in some other part of the United States. If he does not wish to take this, he will be accepted in the Army or in the Navy and allowed to complete his internship in one of these hospitals.

DR. BREED That means that most of the hospitals will have to reduce their internship terms to nine months.

PRESIDENT PAULLIN That is correct. They will not necessarily have to do so, if they can take care of an increased number of interns and give them proper training, they may keep them for twelve months, but they have got to give these interns adequate training—an adequate number of patients to supervise. There are many hospitals in the United States approved for intern training but without interns. Hospitals in the larger cities have an abundance of material or interns, in fact, too many. We hope to distribute to these approved hospitals where interns will get adequate training, some interns who will be available for a year.

DR. BORTZ Mr. Chairman, in Massachusetts the State Medical Society already has a very satisfactory program somewhat similar, in which they are sending teachers into the camps. Iowa also has a set-up of the same kind. Wherever State societies have already organized such a plan, it is not the idea of the Committee on War-Time Graduate Medical Meetings to supersede that but rather to work in cooperation. Where we can in any way assist in elaborating a better program, a unity of action will be preferable.

PRESIDENT PAULLIN Do you also mean to make these courses available for civilians as part of the program?

DR. BORTZ That is right.

BRIGADIER MEAKINS What solution has been arrived at as to the resident staff beyond the intern staff?

PRESIDENT PAULLIN Approximately 20 per cent of the graduates in medicine of the six thousand graduates per annum will have physical disabilities that will keep them out of the military service, this 20 per cent including also women graduates. It is the hope of the Procurement and Assignment Agency to see that most of the resident staff of the hospitals is filled from this group or from others who are physically disqualified, already on duty. Through the Secretary of War and the Surgeon General of the Navy, we have an agreement at the present time by which they will allocate to us, the Procurement and Assignment Agency, a certain number of men who have already completed one year of internship, provided we can establish the essentiality of those men either as assistants in teaching or in rendering necessary medical service to a civilian community. Certain of these men at the present time can be deferred by Selective Service because they are married and have a family and dependents. That is not, however, a very large group.

AMERICAN COLLEGE OF PHYSICIANS, INC
BALANCE SHEET, DECEMBER 31, 1942

<i>General Fund</i>		<i>Liabilities</i>	
<i>Assets</i>	<i>Current</i>	<i>Current</i>	
<i>Current</i>			
Cash in banks and on hand	\$ 21,588 71	Accounts Payable	\$ 115 60
Notes Receivable	30 02	Deferred Income	
Accounts Receivable		Advance Subscriptions, ANNALS OF INTERNAL MEDICINE	14,736 64
Due from Brokers	\$ 1,082 38	Total Current Liabilities	\$ 14,852 24
Advertising	892 84		
American Air Lines	425 00		
Inventory of Keys, Pledges and Frames, at cost	422 80		
Accrued Income on General Fund Investments	290 00		
Accrued Income Due from Endowment Fund Income Account	1,192 91		
Investments at Book Value	116,118 61	Directory Reserve Fund	2,500 00
Insurance Deposit	555 00		
Total Current Assets	\$142,598 27		
<i>Deferred</i>			
1943 Postgraduate Courses	337 14		
<i>Fixed</i>			
College Headquarters, Real Estate	\$57,728 45	General Fund, as annueved	\$ 17,352 24
Less, Allowance for Depreciation	6,000 00		190,569 76
Investment, Real Estate, 404-12 S 42nd Street	9,170 50		
Furniture and Equipment, at cost	11,067 33		
Less, Allowance for Depreciation	6,979 69		
	\$207,922 00		\$207,922 00
		<i>Endowment Fund</i>	
		<i>Liabilities</i>	
Cash in Banks	\$ 214 11	Endowment Fund, Principal	\$136,329 06
Due from Brokers	10,096 88	Accrued Income, Due to General Fund	1,192 91
Accrued Interest	1,192 91		
Investments at Book Value	126,018 07		
	\$137,521 97		
	\$345,443 97		
TOTAL ASSETS		TOTAL LIABILITIES AND FUNDS	

DR FITZ Mr Chairman, I can remember the first time I attended a meeting of the College I was struck with the youth of the College itself and I am wondering if some method can be devised through Dr Bortz' Committee—some method by which we can make the College more attractive to young men It is interesting to note that of the total number of members of the College we should now have almost 27 per cent in the Armed Forces If you take one hundred forty thousand as being the number in the medical profession and then take 27 per cent of that, it will give you about thirty-eight thousand, which is about the number of medical officers as a whole in the Armed Forces Applying this same percentage to the seventy-seven hundred Massachusetts doctors, again you get the figure of about two thousand, which is what we have in the Armed Forces If you break down the figures of candidates for Fellowship and Associateship, again you get the same thing

Most of the candidates for Fellowship are too old to go into the Army and Navy, but when you examine the candidates for Associateship, you get the younger men and a higher proportion are in the Armed Forces All this makes me wonder, with the beautiful scheme you have described of postgraduate education, if we cannot take into consideration means of making membership in the College more attractive to the younger men The postgraduate set-up ought to be directed to the young man rather than the older man

PRESIDENT PAULLIN The actual number of men in the College doing war work is not limited Are there any other remarks?

In closing this session, I should like to thank Mr Loveland, Mr Hegland, Miss Ott and the others for their timely and beneficent help and again the Board of Regents for their untiring and unselfish devotion to duty as evidenced by the attendance at this meeting

The meeting is adjourned

Attest (Signed) E R LOVELAND, *Secretary*

GENERAL FUND

OPERATING STATEMENT

For the Year Ended December 31, 1942

Balance, January 1, 1942		\$166,323 61
Less		
Transfer to Endowment Fund of the Initiation Fees of Life Members	\$ 550 00	
To close Accounts Receivable for Advertising Uncollectible	41 40	591 40
		<hr/>
		\$165,732 21

Summary of Operations for the Year Ended December 31, 1942

<i>Income</i>	
Annual Dues	\$27,982 16
Initiation Fees	18,294 37
Subscriptions, ANNALS OF INTERNAL MEDICINE	32,597 81
Advertising, ANNALS OF INTERNAL MEDICINE	10,895 97
Income from Invested Funds, General	4,414 73
Income from Invested Funds, Endowment	4,564 12
Exhibits, 26th Annual Session	12,987 97
Guest Fees, 26th Annual Session	498 00
Profit on Keys, Pledges and Frames	240 42
Profit on Sale of Investments, net	91 10
Dividend on Perpetual Insurance Deposit	60 00
Sale of 1941 Directory and College History	59 24

TOTAL INCOME

\$112,685 89

Expenses

Salaries	\$30,617 45	
Postage, Telephone and Telegraph	4,419 75	
Office Supplies and Stationery	1,337 86	
Printing	24,968 73	
Traveling Expenses	5,256 28	
College Headquarters		
Maintenance	\$2,156 05	
Heat, Light, Gas and Water	704 84	
Taxes	859 57	
Insurance	121 50	3,841 96
Depreciation on Building, Furniture and Equipment	1,863 31	
Grant to National Research Council	697 16	
1942 Directory Supplement	425 26	
Directory Reserve, 1943	2,500 00	
John Phillips Memorial Prize	262 75	
Research Fellowships	3,600 00	
Investment Counsel and Custodian's Fee	413 89	
Regional Meetings	1,305 46	
Postgraduate Courses	996 64	
Investment, Real Estate, net	687 03	
Other Expenses		
26th Annual Session	\$3,536 01	
Miscellaneous	1,118 80	4,654 81
TOTAL EXPENSES		\$ 87,848 34
Net Income for the Year Ended December 31, 1942		24,837 55
Balance, December 31, 1942		\$190,569 76

ENDOWMENT FUND

OPERATING STATEMENT

For the Year Ended December 31, 1942

Principal Account, January 1, 1942		\$132,586 38
Add		
Life Membership Fees received during 1942	\$2,508 00	
Transfer of Initiation Fees of New Life Members from General Fund	550 00	
Gain on Investment Transactions, net of Losses	684 68	
Total Increase during 1942		3,742 68
Principal Account, December 31, 1942		\$136,329 06
Income Account		
Income from Investments earned during 1942		\$ 4,564 12
Deduct		
Research Fellowships	\$3,600 00	
John Phillips Memorial Prize	262 75	3,862 75
Excess of Income over Expenses, transferred to General Fund Operations for 1942		\$ 701 37

ANNALS OF INTERNAL MEDICINE

VOLUME 18

JUNE, 1943

NUMBER 6

A COMPARISON OF THE METABOLIC EFFECTS OF ISOCALORIC MEALS OF VARYING COMPOSITION, WITH SPECIAL REFERENCE TO THE PREVENTION OF POSTPRANDIAL HYPOGLYCEMIC SYMPTOMS *

By GEORGE W THORN, F A C P, JOHN T QUINBY, M D, and MARSHALL
CLINTON, JR, M D, *Boston, Massachusetts*

INTRODUCTION

EFFICIENCY experts have long recognized the desirability of supplying intermediate supplementary nourishment to maintain the performance of office and factory personnel throughout the working day. Insufficient attention has been given to the fact that the ingestion of a typical American breakfast—one relatively high in carbohydrate and low in protein and fat content—predisposes to midmorning hypoglycemic symptoms. Similarly a luncheon of relatively high carbohydrate content predisposes to hypoglycemia in the midafternoon. During these periods of relative hypoglycemia a definite impairment in performance may be expected. Provision of supplementary nourishment is obviously indicated during these periods except in the case of obese individuals. Circumstances, however, sometimes render the provision of intermediate nourishment either impractical or impossible. Furthermore in certain occupations involving excessive or continued physical labor the ingestion of food without a rest period may initiate undesirable sequelae in some individuals.

The prolonged sense of well-being which follows the ingestion of a meal rich in protein suggested that the intake of increased protein at breakfast might obviate the necessity for midmorning nourishment and might be expected to improve the performance of individuals who do not have ready access to supplementary nourishment at that time. Conn and Newburgh¹

* Presented at the New England Regional Meeting of the American College of Physicians, February 5, 1943, Boston, Massachusetts

From the Department of Medicine, Harvard Medical School, and the Peter Bent Brigham Hospital, Boston

Copyright, 1943, by The American College of Physicians

have reported that blood sugar levels fluctuate widely following that of a high carbohydrate meal, whereas little or no change in blood sugar was observed following the ingestion of a high protein meal. They employed diets which provided equivalent quantities of theoretical glucose. The caloric value of the high protein meal used in this study was approximately double that of the high carbohydrate meal.

With these considerations in mind, studies were undertaken to determine the changes in blood sugar level, caloric distribution, and metabolism which followed the ingestion of isocaloric breakfasts composed of varying proportions of carbohydrate, fat and protein.

METHODS

This study was carried out on a normal male subject who had been used for respiratory studies. For a period of 48 hours prior to each experimental period he was fed a diet composed of carbohydrate 304 gm, protein 69 gm, and fat 113 gm (2509 calories). Following a 14-hour fast, blood sugar level, standard metabolic rate, respiratory quotient and urinary nitrogen excretion were measured. The subject was then given one of the three meals which was consumed within 10 minutes. He remained in bed throughout the experimental period. At hourly intervals after the ingestion of the meal for a period of six hours, blood was taken and urine obtained for analysis. The last 10 minutes of each hour were spent in collecting the subject's expired air in a modified Baily gasometer. Air samples were analyzed in duplicate for oxygen and carbon dioxide by means of a Haldane-Henderson gas analyzer. Differential derivation of calories was made with the aid of Lusk's table². Blood sugar was determined according to the method of Folin and Malmros³ and urinary nitrogen by a modified micro-Kjeldahl method.

The diets employed in this study were isocaloric but of varying carbohydrate, protein and fat composition (table 1). The actual foods used in these diets are presented in tables 2, 3 and 4.

TABLE I
Isocaloric Breakfasts

	CHO gm	Protein gm	Fat gm	Total Calories
High CHO	82	9	4	400
High Protein	26	55	8	396
High Fat	20	8	32	400

OBSERVATIONS

Administration of a high carbohydrate breakfast resulted in a definite increase in the blood sugar level in one hour, followed by a rapid fall to a level of 69 mg per 100 c c at the end of two hours. The fall in blood sugar

TABLE II
High Carbohydrate Breakfast

Item	Quantity gm	CHO gm	Protein gm	Fat gm	Calories
Orange juice	200	20	2	0	88
Cornflakes	12	10	2	0	48
Sugar	9	9	0	0	36
Bread	50	26	4	0	120
Butter	4	0	0	3	27
Jelly	20	15	0	0	60
Milk	30	2	1	1	21
Total	—	82	9	4	400

TABLE III
High Protein Breakfast

Item	Quantity gm	CHO gm	Protein gm	Fat gm	Calories
Skim milk	400	20	14	3	163
Lean beef	30	0	7	3	55
Cottage cheese	160	6	34	2	178
Total	—	26	55	8	396

TABLE IV
High Fat Breakfast

Item	Quantity gm	CHO gm	Protein gm	Fat gm	Calories
Cornflakes	18	15	3	0	72
Cream 19 per cent	160	5	5	32	328
Total	—	20	8	32	400

level was associated with hunger and weakness. Following this episode, the blood sugar level gradually returned to normal (chart 1). Administration of a high protein meal of the same caloric value, on the other hand, was followed by a definite sense of well-being and a maintenance of normal blood sugar level throughout the six-hour experimental period (chart 1). Following a high fat meal, blood sugar levels fell more slowly than after the high carbohydrate meal, reaching a low level of 71 mg in five hours. Hypoglycemic symptoms were noted following the high fat breakfast, but were less severe than following the high carbohydrate meal, and occurred much later (chart 1). There was a striking rise in metabolic rate one hour after the high carbohydrate meal followed by a return to basal level in two hours. After the ingestion of the high protein meal the metabolic rate remained elevated throughout the experimental period. The ingestion of the high fat meal had little influence on metabolic rate (chart 2).

CHANGES IN BLOOD SUGAR FOLLOWING VARIOUS ISOCALORIC MEALS

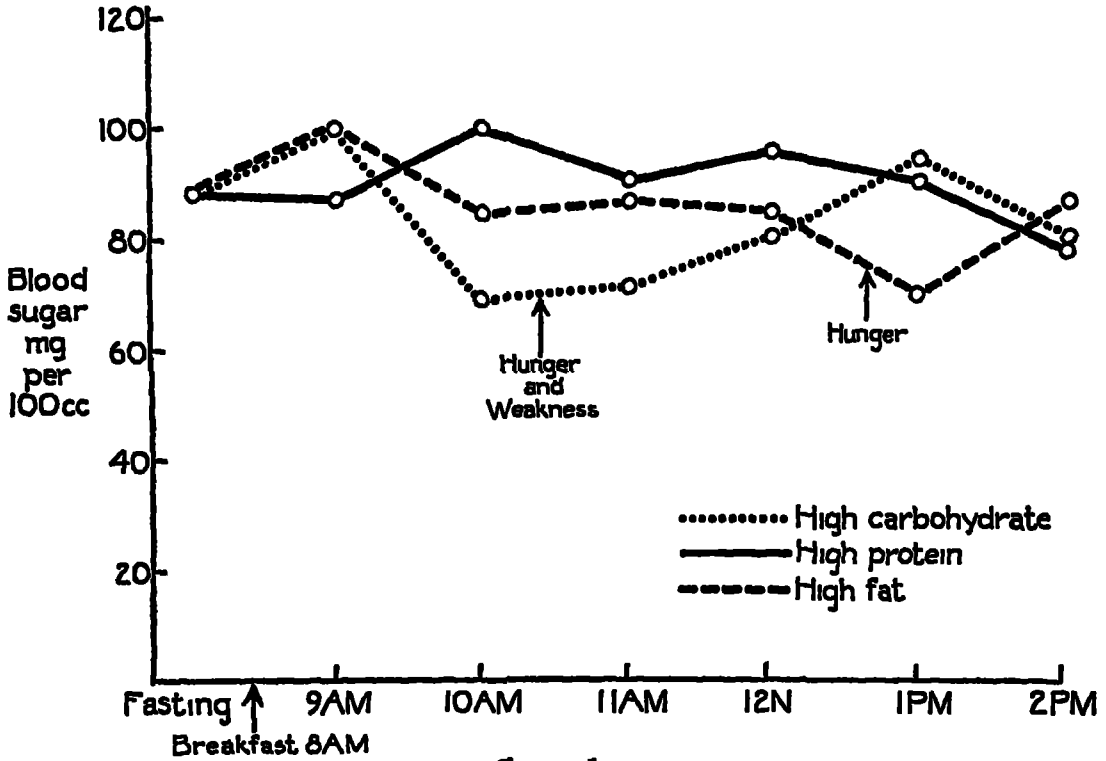


CHART 1.

CHANGES IN METABOLIC RATE FOLLOWING VARIOUS ISOCALORIC MEALS

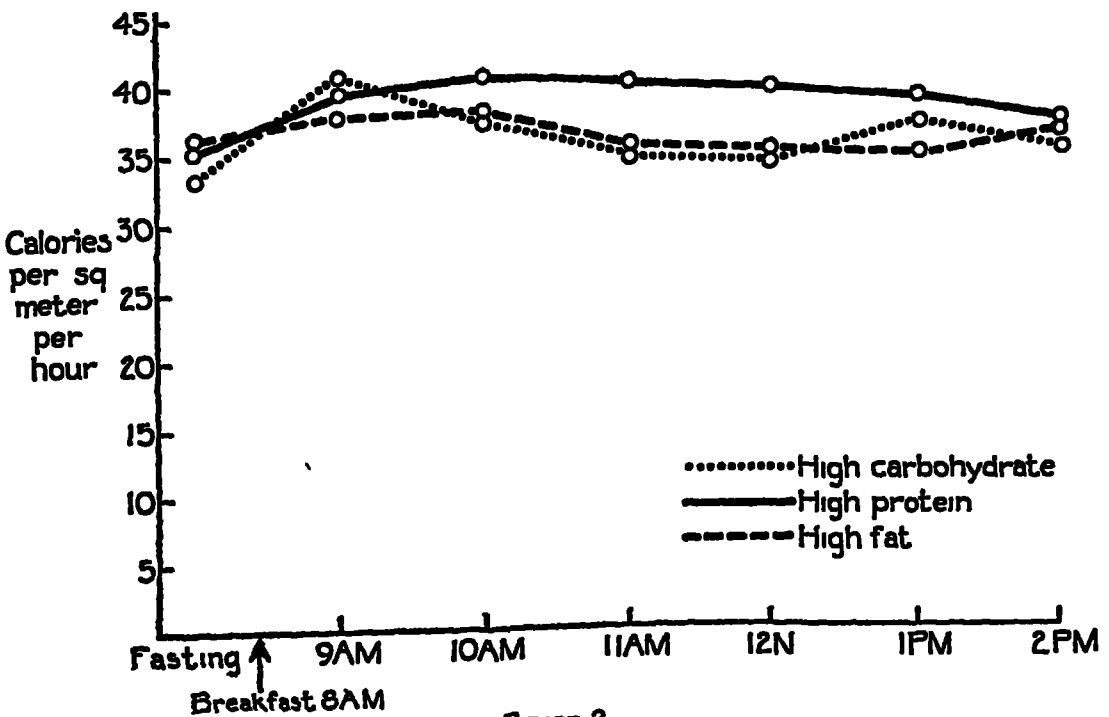


CHART 2

Differential derivation of calories following the ingestion of the various meals is depicted in chart 3. One hour after the ingestion of the high carbohydrate breakfast there was a decided increase in the percentage of total calories derived from carbohydrate, during the remainder of the period, however, there was a gradual decrease in the percentage of calories derived from carbohydrate. The percentage of calories derived from fat increased greatly during the last half of the experimental period. The percentage of

CALORIC CHANGES FOLLOWING VARIOUS ISOCALORIC MEALS

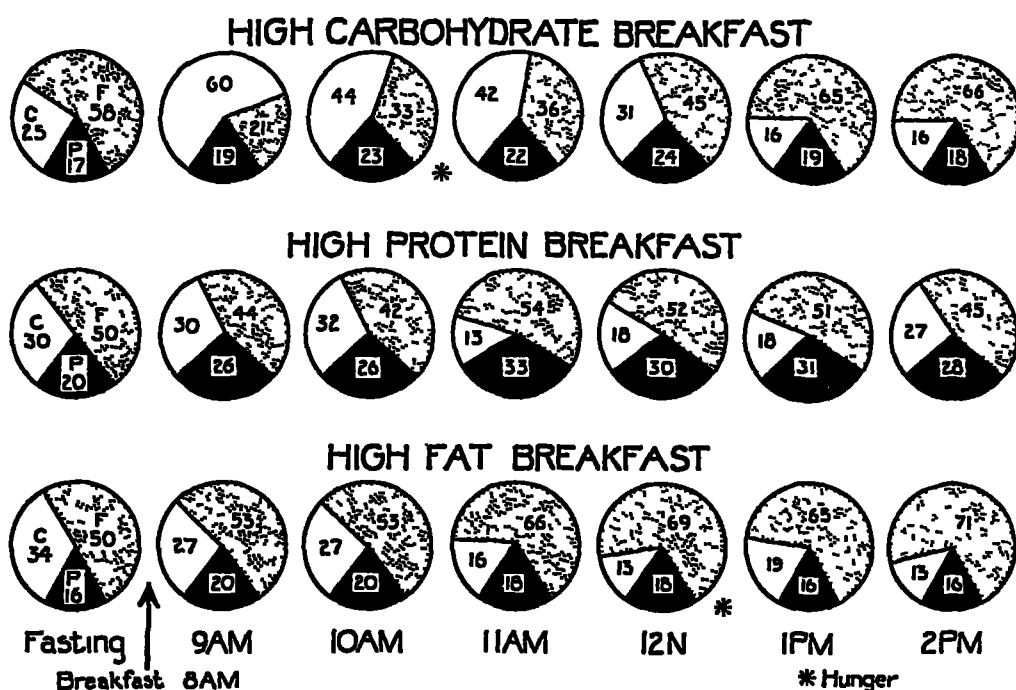


CHART 3

calories derived from protein changed but little following the high carbohydrate meal

Following the ingestion of the high protein meal, a decided increase was noted in the percentage of calories derived from protein. This increase persisted throughout the entire six-hour period. Calories derived from carbohydrate decreased throughout this study, whereas calories derived from fat changed relatively little.

A gradual increase in the percentage of calories derived from fat followed the ingestion of the high fat breakfast. This was associated with a gradual decrease in the calories derived from carbohydrate. No significant change occurred in the percentage of calories derived from protein.

DISCUSSION

Hypoglycemic symptoms are experienced by many individuals two to three hours following meals, symptoms are most likely to occur following the ingestion of a meal of high carbohydrate content. Differential derivation of calories following the high carbohydrate meal used in these studies disclosed a rapid change from predominantly carbohydrate metabolism to predominantly fat metabolism during the second to third hour. This change was taking place at the time hypoglycemic symptoms occurred. It is probable that the inability of many individuals to effect a rapid and smooth transition from a metabolic state involving the utilization of carbohydrate to one utilizing fat as the major source of energy results in the occurrence of hypoglycemic symptoms during this transition.

The occurrence of postprandial hypoglycemic symptoms is known to result in loss of efficiency, and it would appear to be desirable to provide intermediate nourishment at this time for workers despite loss of time and difficulties involved in making suitable arrangements. In some occupations, however, it is not possible to provide intermediate nourishment even though the desirability of such a procedure is evident. The ingestion of a meal of predominantly carbohydrate content, followed in two to three hours by hypoglycemic symptoms which are in turn relieved by the ingestion of more carbohydrate, may result in the establishment of a vicious circle which in turn may lead to obesity. The benefits which might be derived from increased protein in the diet under these circumstances are apparent.

The advantages of employing a diet high in fat and high in protein in the treatment of patients with spontaneous hypoglycemia have been pointed out by Waters,⁴ Clark and Greene,⁵ Conn,⁶ and Swanson and Greene.⁷ The sustained increase in metabolic level which follows the ingestion of protein, in contrast to carbohydrate, may also be advantageous. That a diet of high protein content is not harmful to a normal individual has been demonstrated in a convincing manner by Stefanson⁸ who lived in this country for one year on a diet consisting almost entirely of protein and fat.

The limitation of protein as a source of food for the duration of the war makes the provision of a high protein diet a practical impossibility, but does not prevent the substitution of moderate quantities of protein for carbohydrate in every day diet. For the obese individuals skim milk and cottage cheese may be used advantageously, whole milk, cheese, nuts and soy bean meal may be used in the diets of nonobese individuals.

CONCLUSIONS

- 1 In a normal subject the ingestion of a breakfast high in carbohydrate and low in protein and fat was followed by hypoglycemic symptoms in one to two hours, an isocaloric breakfast high in fat and low in carbohydrate and protein was followed by hypoglycemic symptoms at a later hour, an

isocaloric breakfast high in protein and low in fat and carbohydrate was followed by an improved sense of well-being and no symptoms of hypoglycemia. The blood sugar levels following these three breakfasts corresponded closely to the clinical symptoms.

2 A sustained increase in metabolic rate occurred following the ingestion of the high protein breakfast, a transient increase in metabolic rate followed by a fall below the basal metabolic rate was observed after the ingestion of an isocaloric high carbohydrate breakfast, no significant increase in metabolic level followed the ingestion of an isocaloric high fat breakfast.

3 Following the ingestion of the high carbohydrate breakfast, differential derivation of calories reflected striking fluctuations in the character of the food substances utilized as sources of energy. These fluctuations did not occur following the isocaloric high protein and high fat meals.

4 The disadvantages which may attend the ingestion of meals preponderantly carbohydrate in content are discussed and the possible advantages of an increased protein content are suggested.

The authors are indebted to Miss Marion J. Brian, dietitian in charge of the Metabolic Unit of the Peter Bent Brigham Hospital, for her assistance in this study.

BIBLIOGRAPHY

- 1 CONN, J. W., and NEWBURGH, L. H. The glycemie response to isoglucogenic quantities of protein and carbohydrate, *Jr Clin Invest*, 1936, 15, 665.
- 2 LUSK, G. Animal calorimetry, analysis of the oxidation of mixtures of carbohydrate and fat. A correction, *Jr Biol Chem*, 1924, 81, 41.
- 3 FOLIN, O., and MALVROS, H. An improved form of Folin's micro method for blood sugar determinations, *Jr Biol Chem*, 1929, 92, 115.
- 4 WATERS, W. C., Jr. Spontaneous hypoglycemia. The role of diet in etiology and treatment, *South Med Jr*, 1931, 24, 249.
- 5 CLARK, B. B., and GREENE, J. A. Effect of low carbohydrate diet on glucose tolerance in spontaneous hypoglycemia, *Proc. Soc. Exper. Biol. and Med.*, 1935, 32, 1459.
- 6 CONN, J. W. The advantage of a high protein diet in the treatment of spontaneous hypoglycemia, *Jr Clin Invest*, 1936, 15, 673.
- 7 SWANSON, L. W., and GREENE, J. A. Further observations on the role of diet in the etiology and treatment of spontaneous hypoglycemia, *Jr Lab. and Clin. Med.*, 1941, 26, 828.
- 8 STEFANSON, VILHEJALMUR. Adventures in diet, Harper's, 1935, 668, 1935, 672, 46, and 1936, 677, 178.

THE PROBLEMS OF THE INTERNIST IN THE NAVY *

By R E DUNCAN, F A C P , Captain, (MC), U S N , *Bethesda, Maryland*

Most of the problems which are to be discussed will seem commonplace and in civil practice they would probably be routine matters. However, when considered in the light of the requirements of strenuous and arduous military duties, they present additional issues for the consideration and decision of the internist.

In general, the problems of the naval internist fall into three main categories. First, those concerned with the proper physical selection of personnel, or the elimination of applicants for the service showing physical defects which are of present or may be of future significance. Secondly, the maintenance of physical fitness among our entire personnel. This includes the management and treatment of illness developing in our men, in accordance with the very best medical practice. And thirdly, problems entailing a decision as to whether or not certain diseases are of sufficient import to warrant the retirement of individuals in whom they develop.

The maintenance of an efficient Navy demands personnel who are in the very best of physical condition. It is the duty of our recruiting officers to exercise the greatest of care in selecting personnel. Many medical conditions which are of no great consequence under the ordinary demands of civil pursuits may be of considerable moment when the individual is subjected to the rigorous and exacting duties of naval life. Pulmonary tuberculosis in a preclinical, quiescent or arrested stage is a notable example of such a condition. In civil life, these lesions may never cause disability, but under military conditions involving strenuous physical exertion, long hours and sustained effort and residence in tropical climates, they almost invariably break down.

The importance of incipient hypertension in the naval forces cannot be exaggerated. The medical examiner is repeatedly confronted with the question of accepting a candidate who is otherwise perfectly normal, often of unusually fine physique, whose blood pressure tends to be somewhat elevated. It is appreciated that excitement elevates arterial tension and that is why examiners are directed to take a number of readings under varying conditions. On the other hand, a patient possessing a definite hypertension may at times present a normal blood pressure reading. In fact, the blood pressure of hypertensives is notoriously labile. We know, however, that if the blood pressure rises to abnormal heights it may mean actual hypertension, prehypertension or potential hypertension.

* Presented before the Regional Meeting of the American College of Physicians, Chicago, Ill., November 21, 1942.

Can we afford to turn down the borderline or mild hypertensive in time of war when millions are needed for our military forces? We all know that this man will be good for even most strenuous physical activity for years before definite hypertension appears or becomes a fact. However, if the Navy accepts this candidate and if his blood pressure increases because of the natural course of the disease, the finding of a definite hypertension after the man has been in the service for some time can, by present laws, be construed as caused by or aggravated by service in the Navy. In the case of an officer he will be retired with three quarters of his base pay for the rest of his life. These few remarks show the peculiar angles of the question of incipient hypertension in the Navy.

The question as to the significance of the systolic murmur heard over the mitral or apical regions is ever with the medical examiner. In civilian practice, if after a thorough work up the internist cannot decide whether the murmur is of functional or organic origin, he advises the patient to return for reexamination the next day, week or month, and meanwhile permits the man to carry on all routine physical activities. Not so in the Navy, the examiners may have to decide immediately in case the candidate has come from afar, and usually without the benefit of the electrocardiograph, stethocardiograph, fluoroscope or kymograph. He has to take the full responsibility of deciding the origin of this suspicious systolic murmur in spite of the fact that at times it is quite difficult to make a decision, and when in fact there is still no completely sure way of deciding its origin.

Many other problems having to do with the exclusion of the unfit have to be solved. Is the albuminuria noted in the otherwise desirable young applicant benign or does it have a pathological significance? The question as to the importance of a persistent tachycardia or a cardiac arrhythmia must be carefully evaluated. The consideration of these and other conditions found in applicants for the Naval Service are very practical matters with which the internist must be concerned.

The naval internist plays only a modest part in maintenance of physical fitness among our personnel. The officer trained in public health and sanitation has a much wider field, finding and perfecting methods for the control of epidemic and infectious diseases. In the Navy every officer and man must be physically fit to perform his duties at all times, in all places and under any conditions. Nothing disrupts organization on board ship more than men on the sick list. Take for example a gun crew on any of our ships, here we find team work in its highest state of efficiency. Every man is a specialist in his assigned task. The gun pointer spends many hours finding means to increase the speed with which he can get on his target. The gun captain works to find ways of correlating his group so that extra salvos may be put in the air. The training of this crew takes months. Should some of these men become frequent visitors to the sick list the efficiency of the whole group is gone.

In the management and treatment of the sick our problems are, with few exceptions, no different from those in civil life. Our hospitals are all equipped with every modern facility for proper diagnostic study, therapeutic management and nursing attention. I believe that our naval hospitals furnish the finest example of group practice. There is no cut-throat competition and a helpful cooperative spirit prevails. Our hospital ships and base units are likewise very well equipped, and it is only on small ships on independent duty and some few small outlying stations that the internist may have to rely on his five senses and ingenuity alone. The four quarters of the globe are covered by our Navy and the internist must have a working knowledge of the diseases common to both the tropics and the arctics. He must keep abreast of modern methods of prevention and treatment of these tropical diseases which are of naval importance. The tropical diseases of greatest importance at present which are apt to become of increasing importance are

Malaria (including Blackwater Fever)

Dengue

Dengue-like fevers (Sand Fly Fever)

Dysenteries, both bacillary and amebic

Those of potential importance which may become disabling to naval personnel are

Typhus and other rickettsial diseases

Cholera

Yellow fever

Plague

The relapsing fevers

Infectious jaundice and other leptospiroses

Oroya fever

In our combatant areas, both the African and Southwest Pacific, malaria is more important than all the rest of these tropical diseases combined. The Bureau of Medicine and Surgery has just distributed to all medical officers a pamphlet "Notes on Tropical and Exotic Diseases of Naval Importance." It is well to become acquainted with the treatment of malaria as outlined in this brochure, as the shortage of quinine is rapidly becoming critical.

Although every effort is made to place the highly specialized internist in our larger hospitals where his special training and knowledge will be of most value, this is not always possible. He must realize that although he may have been a heart specialist in civil life, he is now entering another specialty, military medicine, and must adapt himself to it.

I now come to the last group, i.e., those considered for retirement. This is the one in which the problem of the internist in the service and the internist in civil life diverge. One of the most difficult problems the Naval internist has to contend with and one that calls for ability, judgment and service ex-

experience is the question of invaliding from the service many desirable members whose training and experience are invaluable to the service

One of the most distressing things that has come to our attention in the past 20 years is the apparent increase in coronary heart disease. The management of the typical coronary case has a different aspect in the naval service. In civilian life the patient frequently finds it no hardship when told to let up a bit and lead a sensible life. He doesn't lose out and usually adjusts himself very quickly. On the other hand, we have made a hard and fast rule among our officers that no one who has had a frank coronary attack can return to active duty. This may seem cruel and some of you may feel that we are wasting valuable officer material. Consider then the responsibility that falls upon an officer, especially of the line of the Navy. Speed is the essence of everything today. Our ships go faster, our planes fly at increasing speeds. This means that the officer in command of units, or a single unit must have his faculties alert at all times. I can leave it to your imagination what would happen to a number of ships in column, traveling at a speed of 30 knots, should the Commanding Officer of this division or the Commanding Officer of a single unit collapse at his station on the bridge at the time the command was passed to change the course of the formation. It is for this reason that we cannot allow an officer who has had one serious heart attack to assume these spots of great responsibility.

Other types of cardiovascular disease present very much the same picture. How much stress and strain should we allow the individual who has cardiac valvular disease or who is carrying a very high diastolic pressure? How long should we permit this man to go before we call a halt and return him to civil life where he can be rehabilitated in a normal fashion?

Another type of case that is of particular concern to the internist is the peptic ulcer, usually duodenal. The majority of these cases just do not do well in the naval service. There is always the difficulty of obtaining the proper diet and the threat of hemorrhage or perforation. They usually seek duty where they can secure both diet and medical advice. Even after surgery they invariably come back to the internist. These cases eventually have to be invalided from the Service.

The naval internist is against continuing on the active list those individuals requiring substitution therapy, for example hypothyroid states, diabetes, pernicious anemia, or those requiring maintenance doses of drugs such as digitalis and quinidine. In other words, a man who has to depend on a bottle of medicine for his efficiency is not a top flight officer.

In our larger hospitals we are gradually divorcing syphilis and skin from the medical services. This brings up the subject of "Line of Duty" which is most important to every officer and man when he enters upon the sick list. His retired pay or pension will depend upon his ability to establish his line of duty status. The doctor must fairly judge his cases and see that no in-

justices are done and that no means are overlooked to aid patients in clearing up delicate points which may mean everything to them in the future

During our rapid expansion some men have been accepted who have disabilities that later are brought to light. The question as to whether these existed prior to enrollment or whether they were aggravated by service conditions has to be decided. In fairness both to the Government and the man, much thought must be given to these matters.

At this point, this question may properly be asked. What are we going to do with the officers or men with years of service who have great ability and experience? Are their services to be completely thrown away and lost to the Navy? The answer is "Yes" so far as the active list is concerned. However, in times of emergency such as the present one, we have adopted a system which is not unlike that used in civil life. A certain number of these officers and men are recommended for "spot jobs." By spot jobs we mean carefully selected duties in which a man can give the Navy the benefit of his ability and years of experience without subjecting him to the stress and strain of high responsibility. Every attempt is made to keep their duties within the limits of their physical capacity. At a time like this, the Nation and the Navy have the first call on service personnel, whether active or retired, but we as doctors try not to lose sight of the fact that the officer or man also has some equity and that we must consider the dependents of these men.

In time of peace the internist is given every opportunity as he goes along to increase his professional efficiency by postgraduate work in our civil institutions. In this connection, the Navy is especially grateful to the men, mostly Fellows of the College, who have helped train our internists in the field of cardiology, endocrinology, gastroenterology and respiratory diseases. In time of war, these courses are of necessity limited as to number and are shortened. However, it is the policy of the Bureau of Medicine and Surgery to be sure our internists attend as many of the clinics throughout this country as it is physically possible for them to do.

The Medical Department of the Navy is now in a much better position to carry on with its many vital research problems. On October 12, 1942, our new Research Institute was placed in commission as a unit of the National Naval Medical Center in Bethesda, Maryland. It is a magnificent building and contains every type of equipment necessary for scientific research. We were most fortunate in being able to obtain the services of Dr. A. C. Ivy, Professor of Physiology and Pharmacology at Northwestern, as Director of Research for our Institute. In addition to its well trained staff we have the cooperation and active participation of the leading scientists of the country through the medium of the Medical Division of the National Research Council. For reasons of security, I am not at liberty to discuss the many problems under investigation, but I can assure you that they are all most important and pertinent to the war effort, and will result in the saving of many lives.

In this brief review, I have merely attempted to give you an idea of what the internist in the Navy must do in addition to treating his patients. In the past two years our Corps has been augmented by many outstanding internists from all sections of the country. Many are now chiefs of the medical services in our hospitals. All have rapidly adjusted to Service conditions and are doing a splendid job.

Reports coming in from all areas indicate that the Medical Department of the Navy is functioning in a smooth and efficient manner. Just before leaving Washington I saw a report showing that of all the casualties evacuated from the Solomon Islands by plane to other bases, the mortality was less than 1 per cent. Reports coming from our hospital ships and mobile hospital bases located in remote sections of the world have been most gratifying. Yes—we in the Navy face the coming months and years with optimism and confidence in our ability to meet the tasks ahead. We do this with the sure knowledge that we will continue to receive the wholehearted cooperation and support of the American College of Physicians and the profession as a whole.

MEDICAL CARE OF AVIATION PERSONNEL *

By DAVID N W GRANT, Brigadier General, Air Surgeon,
U S Army Air Forces, *Washington, D C*

THE opportunity to speak before the regional meeting of the American College of Physicians, an organization so well known for its pioneer work in elevating and improving the standards of medical practice, is indeed a pleasure. Your college has offered recognition to physicians attaining a certain degree of proficiency, and at the same time, which is perhaps more important, has provided through its scientific sessions and its publications, its valuable postgraduate instruction

Due to the efforts of such organizations, American medicine has indeed made phenomenal advances. Since 1900, the total death rate per 100,000 has been reduced nearly 50 per cent. Deaths from diphtheria have decreased from a rate of 43.5 to 2, typhoid fever from 36 to 1.9, pneumonia from 203 to 80; tuberculosis from 202 to 40. Each year brings notable advances in the prevention and treatment of diseases. Most of you can remember the treatment of diabetes without insulin, pernicious anemia without liver extracts, hemolytic streptococcal infections without sulfanilamide; pneumonia without oxygen, antiserum or the sulfonamides, and the deficiency diseases without specific vitamins. The chapter detailing the control and prevention of yellow fever and malaria is known to all of you. These represent but a few of the advances made in our own lifetime. The list of unsolved medical problems is still long, but they are being solved at an accelerated pace.

With the great need for qualified physicians to meet the present emergency, the Army Air Forces and other components of the armed services have been obliged to draw heavily upon your membership. At present, there are 125 of your fellows and associates in service with the Army Air Forces. You will, undoubtedly, wish to know what your associates are doing and how their services are being utilized. The special training of each physician entering the Air Forces, as indicated by internships, residencies, teaching and hospital affiliations, membership in the various specialty societies, colleges and boards, is carefully evaluated. Following a period of indoctrination and basic training, he is assigned to duty where his training can best be utilized. The Air Forces hospitals, of which there are several hundred (over 400), vary in size from a few beds to those of 2000 beds and more. The chief of the medical, surgical, orthopedic, laboratory, and other professional services, together with many of the younger men on each service, are selected individually. A well-balanced staff is set up, thus utilizing every physician in that field for which he is best qualified. Furthermore, as the organization of these hospitals is perfected, applications will be made to place them on the

* Delivered before a Regional Meeting of the American College of Physicians at Chicago, November 21, 1942

approved list for residencies. Many of our young physicians who have had postgraduate training interrupted, will thus be allowed to continue in recognized postgraduate work, at least for a time. Every effort is being made to encourage young medical officers to take the various boards and colleges while in service. A directive is being sent to the commanding officer of each Air Forces hospital, encouraging the granting of short leaves of absence for the purpose of taking these examinations. Whereas the older men and highly trained specialists will work largely in the hospitals, many of the younger ones will have the opportunity of studying at the School of Aviation Medicine, Randolph Field, Texas. Subsequent to graduation from this school, a year of further experience and training, under supervision, is required before the rating of flight surgeon may be obtained.

War brings to each physician in America the obligation to serve his country in whatever rôle he can best serve, but war also offers a challenge to the physicians of this country to solve its many complex problems. The last war, undoubtedly, emphasized many new medical emergencies, some of which were eagerly studied, investigated, and solved. The pandemic of influenza which swept the world during 1917 and 1918 was a tremendous stimulus to scientific endeavor and research on respiratory diseases. Encephalitis appeared and demanded clinical and laboratory investigation, which furthered the knowledge of this dreaded malady. Even the importance of measles as a serious disease, and the problem of its epidemiology was impressed upon all. The first knowledge regarding the virulence and fatalities occurring in streptococcal pneumonia was acquired during the last war. The many deaths that resulted from gas gangrene stimulated the laboratory workers to prepare its antitoxin. The general interest and recognition of obscure cardiovascular problems were accelerated, and an almost new terminology evolved. Vasomotor instability, effort syndrome, soldier's heart, and neurocirculatory asthenia became common phrases in the medical wards. Exceptional opportunities arose for the study of neuropsychiatric diseases, particularly in the field of functional disorders.

Out of the war came also the stimulus for airplane development, which dramatically demanded that the horizon of medicine be widened to include the almost limitless stratosphere. When man adapts himself to the air and is subjected to great speed, rapid changes in altitude and temperature, and sustained periods at high altitude, numerous physiological disturbances occur. Psychological hazards are present also. Each member of the flying crew faces the possibility of sudden death from the day his training begins. Facing death in the heat of battle is far different, psychologically, from enduring the fear of it during the many months of training. Thus, necessity gave birth and sanction to aviation medicine.

A tremendous amount of work is now being done in the Air Forces Classification Centers in an attempt to evaluate prospective members of the flying crew. The purpose is to select those men with special physical and mental

qualifications, resistant to these stresses. Oxygen indoctrination programs and low-pressure chamber research work is progressing and has already added a tremendous fund of knowledge, invaluable in the care of the flying crew. When the best qualified candidates for the flying crew have been selected and training instituted, the never-ending struggle to adjust man to his new environment begins. Part of this adjustment is accomplished by improved mechanical flying equipment, and part by conditioning the crew both physically and emotionally. The flight surgeon must be keenly aware of the many medical problems peculiar to the flying crew. He must be able to differentiate and interpret the various components of flying fatigue. Flying fatigue is difficult to define, but its results are obvious. It may produce indifference or excitement, fear or bravado, loss of confidence, slowing of reaction time, all of which contribute to accidents and failures in accomplishing a specific mission. It may, generally, be defined as the sum total of physical and emotional disturbances felt by each member of the flying crew. This must be interpreted individually, as it varies widely. It consists of the actual physical fatigue, the stress of psychological hazards, the monotony and boredom of the training grind, unpleasant living conditions, lack of recreation, irregular hours, insufficient sleep due to operational necessity or excessive personal indulgence, physiological changes due to altitude or flying conditions, and probably many more factors. These stresses affect not only the psychologically unstable individual, but are manifest in all members of the crew in varying degrees. The flight surgeon must detect and identify these symptoms early, correcting the particular phase of fatigue involved. In short, he must live, eat, play, and fly with the crew to fulfill properly his rôle as physician, father-confessor, and friend, for it is upon him that the responsibility rests of keeping the crew fit to fly.

Air evacuation of casualties is another phase of aviation medicine which will play a considerable rôle in this war. Studies are being made with regard to the types of cases which can be moved by air and to what altitudes. It must be determined how soon casualties of various types can be evacuated to this country, thus saving personnel, supplies, and shipping. That large numbers of troops, both ground and air forces, will be moved in this manner is certain. This is but another of a thousand pioneer problems undertaken by the Army Air Forces.

Today, this challenge to physicians is greater than during the last war for the opportunity now is unique. Never before in history has a thoroughly mixed population, taken from all sections of this country, been transported to every distant corner of the world. The diseases, epidemics, and medical problems of all countries, climates, and peoples are now ours to solve. Let every physician in America, whether he serves his country with the armed forces or at home, accept this challenge, and though his sacrifice is great, make his contribution to the advancement of medical knowledge during this crisis.

PEPTIC ULCER IN THE UNITED STATES NAVY *

By VICTOR W LOGAN, M D , F A C P , Lt Comdr (MC) U S N R , and
PAUL W BRANSFORD, M D , Lt (j g) (MC) U S N ,
Philadelphia, Pennsylvania

THIRTY-FIVE years ago the Surgeon General of the Navy listed in his Annual Report but two admissions to the sick list under gastric ulcer, or "ulcus gastricum" as it was then termed in the official nomenclature. Since that time there has been a steady rise in the incidence of all peptic ulcers. Thus, five duodenal and 21 gastric ulcers were listed in 1912, and 28 duodenal and 35 gastric ulcers in 1920.

In the accompanying table (table 1) the trend of U S Navy admission rates for duodenal ulcer is shown from 1924 up to the last prewar year,

TABLE I

Admission Rates per 100,000		Ulcer, duodenum	U S Navy
1924	41	1933	123
1925	62	1934	136
1926	79	1935	145
1927	89	1937	114
1928	95	1938	91
1929	104	1939	92
1932	110	1940	117

1940 Kantor¹ gives somewhat different figures for the U S Army, asserting that in 1930 the admission rate for duodenal ulcer was 110, rising to 160 in 1939. Just why the Army should have a higher rate than the Navy for the same peacetime decade is not clear. Nor is it clear why in 1935 the Navy had its highest rate of ulcer admissions.

The most recent statistics available are those contained in the Annual Report of the Surgeon General of the U S Navy for the year 1940. As will be seen in table 2, ulcer, duodenum, ranks seventh among diseases of the digestive system in admissions to the sick list, but it ranks first in number of sick days per case.

Of the 305 peptic ulcers reported, 15 per cent were gastric ulcers. This high incidence of gastric ulcer is identical with that given by Allison and Thomas² for the Royal Navy in the same year, but it is markedly at variance with the recently reported findings of Chamberlin³ and Berk⁴ of the U S Army, and Urquhart and his associates⁵ of the Canadian Expeditionary Force. For gastric ulcers constituted less than 5 per cent of the peptic ulcers in each of the latter series.

* Presented before the Fifth Annual Regional Meeting of the American College of Physicians, Philadelphia Pa., October 23, 1942.

(Note: Authorization has been obtained from the Surgeon General for publication.)

The writers of this paper wish to state that the opinions and assertions contained herein are private ones and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

TABLE II
Class 3 Diseases of the Digestive System U S Navy, 1940

Disease	Number of New Admissions	Admission Rate per 100,000	Sick Days per Case
1 Gastroenteritis, acute	2282	1126	5 1
2 Appendicitis, acute	2263	1117	22 8
3 Hemorrhoids	678	335	17 2
4 Appendicitis, chronic	630	311	25 9
5 Gastritis, acute	554	273	7 7
6 Cholangitis, acute	480	237	22 0
7 Ulcer, duodenum	238	117	57 1
Ulcer, stomach	39	19	49 7
Ulcer, duodenum, perforated	22	11	56 4
Ulcer, stomach, perforated	6	3	—
All peptic ulcers	305	155	—

Had all the peptic ulcer patients of the Navy in 1940 been concentrated in one hospital, a ward of 47 beds would have been occupied continuously throughout the year. Further, peptic ulcer in 1940 occasioned the invaliding from the service of 20 per cent of those admitted with this disease, 61 enlisted men and 7 officers—more invalidings from the service than from asthma, or diabetes, or rheumatic fever, or arterial hypertension, or nephritis. Similarly, the British medical writers have stressed the seriousness of the peptic ulcer problem in the armed forces. Sir Arthur Hurst stated that “dyspepsia” in 1940 accounted for 17 per cent of all admissions to the military hospitals of England, and in May 1941 an editorial in the *Canadian Medical Association Journal* went so far as to state that peptic ulcer was the major disability of wartime.

Palmer⁷ has recently reviewed the British figures and compared them to the findings of our own Army surgeons. There is a remarkable similarity in the statistical facts, and, in essence, they find that digestive diseases account for about 15 per cent of all medical patients admitted to military hospitals, of

TABLE III
Ulcer Cases in Military Hospitals (British figures from Brockbank², United States and Canadian figures from Chamberlin,⁸ Berk,⁹ and Urquhart⁴)

Author	Hospital	Total G I Admissions	% Ulcer	% Duodenal
British				
Allison and Thomas	Naval	100	45	85
Brockbank	Military	931	42.5	84
Graham and Kerr	Military	246	64	85
Maingot	General	256	56	89
Morris	Military	500	50	—
Payne and Newman	E M S	287	89	80
Spillane	Military	200	32	84
Willcox	E M S	41	69	73
United States and Canadian				
Chamberlin	Lawson Gen	316	31	95
Berk	Tilton Gen	113	43	94
Urquhart	15th Can Gen	—	—	96

these, about 40 to 50 per cent are due to peptic ulcer, and of these ulcers, the British find that 85 per cent are duodenal, whereas the Americans and Canadians report 96 per cent duodenal. The exact figures are given in table 3

PEPTIC ULCER IN THE PHILADELPHIA NAVAL HOSPITAL

The admission rate for peptic ulcer cases among active service men in this hospital is not higher than 1 per cent, but even though our series is small, it may be profitable to review the experience of the staff with the ulcer patients who have come to us in the eight war-months ending September 30, 1942. Our data are summarized in tables 4 and 5

TABLE IV
Peptic Ulcer at the Philadelphia Naval Hospital,
8 months ending September 30, 1942

Ulcer, duodenum		23 cases (85%)
a Perforated	4	
b Hemorrhage	1	
Ulcer, stomach		4 cases (15%)
Total Peptic Ulcers		27 cases (100%)
Ulcers existing prior to entry	8	(30%)
Officers with ulcer	3	
Enlisted men with ulcer	24	

TABLE V
Disposition of Peptic Ulcer Patients, U S N H, Philadelphia,
8 months ending September 30, 1942

Discharged to duty	7	(Officers 0, CPO 1, Men 6)
Limited to duty ashore only	5	(Officers 2, CPO 3, Men 0)
Invalided from the service	15	(Officers 1, CPO 1, Men 13)
Total	27	(Officers 3, CPO 5, Men 19)

On reviewing the service records of the group, several types stand out

1 The recruit whose very entry into the service precipitates his ulcer. With no prior ulcer history, his symptoms appear within one month.

2 The recruit who has failed to recognize his previous ulcer episodes. His symptoms appear within six months.

3 The recruit who knows he has an ulcer, and who invariably remarks "No one asked me if I had an ulcer when I enlisted." (One man had a six inch upper right rectus scar, the result of a perforation in 1932.)

4 Men who have served the Navy for some time and develop an ulcer in the normal course of events.

5 The retired chief petty officer who is called back to active duty at an age when readjustment is not easy.

The three officers with whom we had to deal fell into the first and fourth categories.

* In contrast to U S Veteran Administration patients who have a high admission rate for peptic ulcer.

Table 5 records the disposition of our 27 cases. Three of the invalidings represented errors of judgment in previous discharges to duty. One officer and one of the men, sent back to duty after satisfactory response to treatment, relapsed within one week. One retired chief petty officer, who had been called back to active duty, developed an ulcer late in 1941, but he improved after hospitalization and was sent to limited shore duty. In three weeks he relapsed and had to be retired unfit for mobilization afloat or ashore.

THE DISPOSITION OF ULCER PATIENTS IN MILITARY MEDICINE

Disposition of the ulcer patient in the naval service is entrusted to the medical officer in charge of the case, provided he feels that the man is fit to return to duty. Otherwise he must submit the facts to a Board of Medical Survey which makes recommendations, subject to the approval of the Bureau of Medicine and Surgery.

As we have seen, in past years only 20 per cent of those suffering from ulcer have been invalided from the U S Naval Service. The British, early in the war, according to Brockbank,³ sent most of the men who responded to treatment back to duty. However, so many relapsed that the War Office had to issue a ruling in the letter of February 1, 1941, giving these causes for invaliding from service: (1) A long chronic history of ulcer indigestion, with anemia, loss of weight, or tenderness (roentgen-ray confirmation not obligatory); (2) Active symptoms, with a lesion proved by roentgen-ray; (3) A history of perforation or massive hemorrhage.

Urquhart⁴ of the Canadian Expeditionary Force, after having had the unpleasant experience of readmitting, within three months, 26 out of 40 men sent back to duty, came to the conclusion that "all cases of active duodenal ulcer should be invalided." Smellie,⁵ in a recent article, agrees with him, saying "Whenever the diagnosis of ulcer has been established, the soldier should be invalided, and returned to civilian life in the shortest possible time."

Chamberlin⁶ of the Lawson General Hospital in Atlanta states "The man with a peptic ulcer is unfit for military service." On his hospital service, all the enlisted men with ulcer and 16 out of 18 officers with ulcer were invalided from the Army. Only two officers were retained for assignment to limited duty.

Palmer,⁷ on the other hand, feels that "under proper conditions, patients with peptic ulcer are capable of performing many important tasks. Hence they may be assigned to limited duty within the continental United States, under conditions permitting them to carry on such dietary and other therapy as may be necessary."

Allison and Thomas² of the Royal Navy distinguish between different types of ulcer cases. They state that "when pain is characteristic, and has recurred over a long period, there are strong reasons for invaliding," and "that men who have suffered from hemorrhage or perforation, even if recovery is complete, should be invalided." Otherwise they feel that patients

who have done well under treatment may be returned to duty with recommendation for shore service or for ships carrying a medical officer

DISCUSSION

What then should be our policy in dealing with the ulcer problem in the United States Navy? First, we must make greater efforts to discover and eliminate the man who has a peptic ulcer before his entry into the service. This can be accomplished only through the diligence of the medical officers who are charged with the examination of prospective naval personnel. Recent health records have carried this sworn statement "I hereby certify that I do not suffer from venereal disease, bed-wetting, asthma, hay fever, rheumatism, fits or insanity, flat or low arches." Would it not be well to add ulcer and chronic indigestion?

It would be folly for us to ignore the experience of the British and make the mistakes against which we have been warned. This will mean that whereas formerly we sent 80 per cent of our ulcer patients back to duty in peacetime, we must now exercise the utmost caution in discharging these men even to limited duty. It is our belief that the best interests of both the patient and the naval service demand that no officer or enlisted man, suffering from peptic ulcer, should be discharged to duty without the recommendation of a Board of Medical Survey, approved by the Bureau of Medicine and Surgery. The Board of Medical Survey, further, should recommend for return to duty only those ulcer patients who are definitely indispensable and whose case histories are most innocuous.

In considering the question of fitness for duty, it must be remembered that response to treatment in the hospital is not sufficient justification for making a prognosis. Will power to resist some of the pleasures of leave and liberty, intelligence sufficient to follow a convalescent ulcer diet at the regular mess, and emotional stability are elementary requisites for the exceptional case of healed peptic ulcer whom we may, with any degree of hope, send back to full duty. For this reason, before discharge we feel that it is wise to allow the man liberty several times, and, after the principles of the ulcer diet have been explained to him, to insist that he choose his food in the regular mess for some time. Patients who have had a perforation, a massive hemorrhage, or gastric surgery should, probably, always be invalided from the service.

Occasionally the urgency of the times may justify risking a recurrence. As an illustration, we were about to recommend the discharge of a man from the service, when, by chance, one of his officers called to see him. We were informed that this patient was one of 20 men capable of teaching the repair of a secret precision instrument. Had we deprived the Navy of his services many hundreds of lives might have been lost. Likewise, Officers and Chief Petty Officers who have special skills acquired from long naval service are not to be discarded lightly in these times. They should be considered for

limited duty ashore, where they may live with their families and run no greater risk of recurrence than if they were in civilian life

Aside from these special cases, there is little reason for retaining the ulcer patient, whether he be officer or enlisted man. From the evidence at hand, the odds are that he will have a recurrence on active duty. It is all very well to say that on our large ships there are able surgeons and ample facilities for handling ulcer emergencies, but we doubt whether the medical officer who treated the man in our series for massive hemorrhage at sea, while expecting contact with the enemy, would agree.

SUMMARY

1 The statistics on peptic ulcer from the Annual Reports of the Surgeon General, U S Navy, from 1917 to 1940 are reviewed and discussed

2 Twenty-seven cases of peptic ulcer that were discharged from the U S Naval Hospital, Philadelphia, Pa, during the eight months ending September 30, 1942, are analyzed

3 The question of disposition of the ulcer patient in military life is presented with points of view from various observers of the problem

4 The authors conclude that no naval officer or enlisted man suffering from peptic ulcer should be discharged to duty without the recommendation of a Board of Medical Survey (subject to the approval of the Bureau of Medicine and Surgery). It is also stated that the Board of Medical Survey should recommend for return to duty, only those patients who are most indispensable and whose case histories are most innocuous

BIBLIOGRAPHY

- 1 KANTOR, JOHN L. Digestive disease and military service, Jr Am Med Assoc, 1942, cxx, 254-261
- 2 ALLISON, R S, and THOMAS, A R. Peptic ulcer in the Royal Navy, symptoms and pathology, Lancet, 1941, i, 565
- 3 BROCKBANK, WM. The dyspeptic soldier, Lancet, 1942, i, 39-42
- 4 URQUHART, R W I, ET AL. The peptic ulcer problem, Canad Med Assoc Jr, 1941, xlv, 391
- 5 SMELLIE, J M. Gastric disorders in the Army, Lancet, 1942, i, 322
- 6 CHAMBERLIN, D P. Peptic ulcer and irritable colon in the Army, Am Jr Digest Dis, 1942, ix, 245-248
- 7 PALMER, WALTER L. The stomach and military service, Jr Am Med Assoc, 1942, cxix, 1155-1159
- 8 BERK, J EDWARD. Quoted by Chamberlin⁶

MILITARY NEUROPSYCHIATRY IN THE PRESENT WAR*

By E H PARSONS, M D, † *Atlanta, Georgia*

I

MILITARY medicine reflects both the military operations of the period considered and the current stage of medical advance. Each war has presented its own peculiar medical problems, some of which were not solved until after hostilities had ceased, some of which were solved brilliantly during the heat of battle, and others of which still remain. The scurvy of Washington's troops, the dysentery of both armies in 1861-1865, the typhoid of 1898, and the influenza of 1918 are as identifying in military medicine as are the tactics of the campaigns in which these medical problems arose. If one considers only the official reports of these wars, psychiatric problems either did not exist or were inconsequential in the American Armies until 1917. Actually, of course, these disorders did occur, were occasionally recognized and rarely reported.

As early as 1856¹ there were enough psychotic American soldiers, sailors, and marines to warrant the founding of what is now known as St Elizabeth's Hospital in Washington, D C. Psychiatric disorders, however, were not a military problem in any army until the Russo-Japanese War when the Russians first reported large numbers of mental disorders, particularly among the officer personnel engaged in that brief war.² The Japanese reported none. The German Army, prior to 1914, recognized such disorders and characteristic Teutonic studies were begun. The Surgeons General of the U S Army and the U S Navy started postgraduate study in psychiatry for medical officers at St Elizabeth's Hospital in 1909.³ The late Dr W A White, then Superintendent of that institution, may well be considered the father of military psychiatry in this country. Kay,⁴ studying the British Army in 1912, found, apparently to his surprise, that mental disorders were present in a significant number even during times of peace. He summarized his studies in what was then a satisfactory statement, "Insanity is invariably increased as a result of war." King,⁵ in 1914, reviewed the neuropsychiatric state of the U S Army and made several observations which were, unfortunately, lost sight of in the war which followed three years later.

World War I, that dress rehearsal for today's conflict, brought functional nervous disorders into prominence as a by-product of war. Sutton⁶ has expressed the belief that psychiatry made its first post-Kraepelinian prog-

* Read before Regional Meeting, American College of Physicians, Atlanta, Georgia, March 14, 1942. Received for publication April 22, 1942.

† Major, Medical Corps, U S, Chief of Neuropsychiatric Service, Lawson General Hospital, Atlanta, Georgia.

ress with the stimulus of the World War I case load. Whether one can consider this huge case load with its accompanying social and economic results as beneficial or not is beyond the scope of this presentation. It is clear, however, that more attention was directed upon disorders of the central nervous system, both functional and organic, during and after the first World War than previously.

That unfortunate term, "shell shock," made its appearance in both lay and medical literature during this period. One wonders if psychiatry, and military psychiatry in particular, will ever live down this expression. Many of the most prominent observers of that day subscribed to compression, air pressure, high explosives and similar bizarre etiological explanations for cases which were, in civil life, recognized as clear-cut psychoneurotic reactions.⁶ Hurst,⁷ Osler,⁸ and others of equal ability subscribed to this then popular explanation.

II

The Boer War was characterized by depression states.⁴ The Russo-Japanese War² was characterized by alcoholic reactions, confusion states and gross hysterias. My associates and I have been interested in observing the incidence and characteristics of the neuropsychiatric disorders we have encountered in the U S Army during the present war. We can present at this time only a preliminary report based upon study of our first 200 cases. These data permit an indication rather than a final determination. These cases are shown in table 1. It is evident that more than 70 per cent of our cases fall into one of the following four groups: neuroses, psychoses, organic neurological or psychopathic personality disorders.

TABLE I
Military Neuropsychiatric Admission

	No	Per cent
Neuroses	43	22
Psychoses	37	18
Neurological	35	17
Psychopaths	28	14
Miscellaneous	13	7
No NP disease	13	7
No disease	10	5
Mental deficiency	9	4
Epilepsy	7	3
Alcoholism	5	3
Total	200	100

Neuroses We have observed the usual varieties of psychoneuroses in this group but the most common neurotic reaction occurring here is that characterized by anxiety, depression, agitation, apprehension, suicidal drive, loss of energy, mental retardation, confusion, indecisiveness, insomnia and uncontrollable weeping. Table 2 shows the incidence of these findings in 20 cases of this series. Anxiety was present in each case as was depression. Eleven of the 20 cases were regarded as markedly suicidal. Three had made

suicidal attempts prior to arriving at the hospital, one by firing his service automatic into his left chest, another by leaping into a fire, and the third by cutting his wrist. This group was further of significance in that 18 of the 20 were officers and the other two were non-commissioned officers. Three

TABLE II
Anxiety-Depression Neuroses

No of Cases	No	Per cent
Symptom	20	100
Anxiety	20	100
Depression	20	100
Retardation	20	100
Loss of energy	20	100
Apprehension	18	90
Suicidal drive	11	55
Confusion	10	50

were medical officers, three were chaplains and the remainder were from various arms and branches of the service. Physical examination and comprehensive laboratory and special examination survey procedures revealed nothing of clinical significance in any of these cases. The mean age of this group was approximately 34 years. This is 10 years greater than the mean age of the entire series. Longitudinal life histories and personality studies on this group of cases showed underlying personalities uniformly characterized by meticulousness, inadequacies, perfectionism and dependence upon others for the most trivial of life decisions. In each case of this group, the onset of the syndrome was relatively rapid, rarely extending over three weeks and, under therapy, recovery has been almost as dramatic. It should be noted that relief from active military duty has been a therapeutic as well as an administrative procedure in each of these cases.

Psychoses The psychoses observed in this series have been predominantly schizophrenic in nature. These reactions have been most frequently encountered in young soldiers whose military service has varied from one day to three months. Schizophrenia, like measles, is a disease of recruits. Of the 37 psychotic patients studied in this series, 33 were schizophrenics. This group is shown in table 3. It will be noted that 10 of these cases

TABLE III
Schizophrenia

No of Cases	No	Per cent
Ill prior to Army service	33	100
Previously committed	10	31
Previous shock therapy	7	21
Acute Schizoids	4	12
Schizophrenic (chronic)	11	33
	22	67

had been known to the family as mentally ill prior to entrance into the military service. Of these 10 cases, seven had been previously committed to institutions for mental care and treatment. Four of the previously com-

mitted cases had been discharged from other hospitals as "recovered" following the use of one of the varieties of shock therapy

Eleven of these cases presented an acute schizophrenic illness characterized by withdrawal, negativism, mutism, autistic thinking, severe mental confusion, preoccupation, paranoid delusional content, accusatory auditory hallucinatory experiences, affective impoverishment and loss of insight. The underlying personality in these cases was characterized by sensitiveness, shyness, lack of self-confidence, deficient sex drive and immaturity. Under a rather simple regimen of protection, reassurance and graduated activity, all of this group recovered from the acute episode. These cases, too, were discharged from the military service for both therapeutic and administrative reasons. One of these cases was a young officer; the remainder were privates. The mean age of the schizophrenic group was approximately 24 years as was that of the smaller group who made rapid recoveries and of the total series of both neurological and psychiatric cases.

Organic-Neurological In this group the traumatic cases predominate as a medical reflection of military mechanization. These cases are not battle injuries but represent truck, tank, automobile and airplane accidents. A smaller number of this group are peripheral neuritic syndromes such as Bell's palsy and toxic neuritides following a variety of causative agents. In the combat zone the organic, particularly the traumatic, group would be considerably larger and, with accelerated war preparation, may increase in the zone of the interior.

Psychopathic Personality Disorders This group of unpleasant cases is present in our series in about the usual incidence rate of peace time. Study of this group has shown us nothing peculiar to the present war period.

III

We have studied neuropsychiatric cases occurring in the U S Army during a mobilization and a war period. None of our cases is from the combat zone. The psychic stresses to which our patients have been subjected have been: (1) separation from home, familiar environs and the personal reassurance of the family, (2) strange occupations, (3) large responsibilities (in the case of officers), (4) fatigue, (5) impersonality of environment, (6) regulation of activities with loss of personal liberties, (7) strict accountability, and (8) anticipation of personal injury or death. These are the basic stresses of the military recruit in any period. The personality who was meticulous, perfectionistic, dependent upon others for constant reassurance and personal guidance could only develop an anxiety state when subjected to the radical change from his civil niche to military life. The Swiss Army mobilized during World War I developed this syndrome without firing a round.⁹ The German Army has had this same problem¹⁰ and undoubtedly still does, although no information is now available on the point.

The British Army has divided its military psychiatry in the present war into the pre-Dunkirk and the post-Dunkirk periods¹¹ In the earlier period, mental deficiencies, epileptics and anxieties predominated With Dunkirk, however, exhaustion deliria and acute confusion states prevailed The Canadian Army studied by Baillie¹² showed, in the earlier stages of this war, a preponderance of psychopathic personalities, mental deficiencies, organic cases and epilepsy His series showed a low incidence rate of neuroses and psychoses Baillie's data are comparable to ours in that he studied 200 cases in the Canadian Army preparation period of the war The Canadian, according to some observers,¹³ has presented more psychosomatic manifestations than has the U S Army group The exact cause for these differences is not evident at this time

In the cases which we have studied, the psychoneurotic syndrome of anxiety with depression has predominated as the neurosis of this war The psychodynamics of this syndrome appear, upon the preliminary data now available to us, to be essentially that of an insecure, worrying perfectionistic personality placed in a position of what is, to him, intolerable stress with resultant anxiety, depression, retardation and related symptoms

Schizophrenia is the psychosis of major military significance now as it has been since the disorder was first recognized In the U S Army of peace time, this disorder is approximately three times as common as it is in the comparable age and sex group in civil life¹⁴ This phenomenon has been studied several years by various workers Hoffman, Parsons and Hagan¹⁵ reported a 12 year follow-up study of these cases with findings which indicate less chronicity of this disorder among military personnel than among young men in civil life Duval and Hoffman continued these studies observing that acute schizophrenic episodes with rapid onset and early recovery occurred in 47 per cent of their military cases Anderson¹⁷ is engaged in a similar study of these cases and suggests that they are not schizophrenia in the usual or dementia praecox concept The syndrome is clearly a psychologic escape mechanism which occurs in shy, timid, immature young men inducted into the military service or enlisted for the misguided purpose of "being made a man of"

We have not utilized shock therapy in the treatment of schizophrenia Twelve per cent of our cases had previously "recovered" after treatment by this method One-third of our cases have made what appears to be complete recoveries at the end of relatively brief hospitalization, and an additional one-third were markedly improved In our practice, therefore, shock therapy appears unwarranted

Neurological disorders are, in the military service, predominantly traumatic in origin Disseminated sclerosis, however, is not infrequently encountered as are a few brain tumors and a considerable number of peripheral neuritides An increasing number of traumatic neurological cases is expected with accelerated training of mechanized forces and battle casualties

The psychopathic personality is a constant military as well as civil problem. Cleckley¹⁸ has recently reviewed this problem in a most comprehensive manner. Porter,¹⁹ Parsons, Ewalt and Peake, and Hall²⁰ have presented the military inaptitude of this group. There is a unanimity of opinion that these individuals cannot be utilized in any part of the military service. We feel that they cannot be treated, and we present no medical solution to this most important psychiatric problem today.

IV

Our preliminary report deals with 200 military neuropsychiatric cases hospitalized during the period of preparation and early months of the present war. We find that the characteristic neurosis of this period is anxiety with depression. The psychosis is schizophrenic in nature with one-third of the cases presenting acute episodes which subside quickly. Traumatic neurological disorders have been prominent in our cases, and we anticipate increasing prominence.

BIBLIOGRAPHY

- 1 PARSONS, E H, and OVERHOLSER, W. Saint Elizabeth's Hospital, Mil Surg, 1938, lxxxiii, 227
- 2 STEIDA, J. Ueber Geisteskrankheiten im russischen Heer während des russisch-japanischen Krieges, Zentralbl f Nerven u Psychiat, 1906, xxix, 875-880
- 3 SUTTON, D G. Psychiatry in the armed forces, Psychiatry, 1939, ii, 1
- 4 KAY, A G. Insanity in the Army during peace and war and its treatment, Jr Roy Army Med Corps, 1912, xviii, 146
- 5 KING, E. Bull Surgeon General's Office, War Department, Washington, D C, 1914
- 6 MILLER, E. The neuroses in war, 1940, The Macmillan Co, New York
- 7 HURST, A F. Medical diseases of the war, 1917, Edward Arnold, London
- 8 OSLER, WM. Editorial, the Lancet, 1917. Quoted by MILLER, E. The neuroses in war, 1940, The Macmillan Co, New York
- 9 STRASSER, C. Ueber Unfall- und Militarneurosen, Kor-Pbl f schweiz Aerzte, 1917, xlvii, 257-274
- 10 UHLMANN, FR. Die Mobilisationspsychosen in der schweizer Armee, Kor-Pbl f schweiz Aerzte, 1918, xlviii, 345-351
- 11 DEBENHAM, G, HILL, D, SARGANT, W, and SLATTER, E. Treatment of war neuroses, Lancet, 1941, i, 107
- 12 BAILLIE, W. A summary of 200 neurological and psychiatric admissions from the Canadian Army Service Forces, Am Jr Psychiat, 1941, xcvii, 753
- 13 WILLCOX, P H. Gastric disorders in the services, Brit Med Jr, 1940, i, 1008
- 14 POLLOCK, H M. Personal Communication, 1938
- 15 HOFFMAN, J L, PARSONS, E H, and HAGAN, M W. The post-hospital adaptation of a selected group of patients with dementia praecox, Jr Nerv and Ment Dis, 1941, xciii, 705
- 16 DUVAL, A M, and HOFFMAN, J L. Dementia praecox in military life as compared with dementia praecox in civil life, War Med, 1941, i, 854
- 17 ANDERSON, A R. Personal Communication.
- 18 CLECKLEY, H. The mask of sanity, 1941, C V Mosby Co, St Louis
- 19 PORTER, W C. The military psychiatrist at work, Am Jr Psychiat, 1941, xcviii, 317
- 20 HALL, R W. Peculiar personalities, War Med, 1941, i, 383

PSYCHONEUROSES IN WAR TIME*

By LLOYD H ZIEGLER, M D , *Wauwatosa, Wisconsin*

IN the Dialogues of Plato, written more than 2000 years ago, one finds the following description of Herodicus

"He had a mortal disease which he perpetually tended, and as recovery was out of the question, he passed his entire life as a valetudinarian, he could do nothing but attend upon himself, and was in constant torment whenever he departed in anything from his usual regimen, and so dying hard, by the help of science, he struggled on to an old age, a rare reward of his skill!"

This description suggests to us that the disorders of human nature have not changed much since ancient times. No modern diagnostic term, such as psychoneurosis, can do better than such a descriptive paragraph.

Internists and surgeons, finding no disease of the body in disabled and complaining patients, are inclined to call the disorder a psychoneurosis. The psychiatrist does not arrive at his conclusion in this negative way. He has in mind a positive syndrome that may be deduced, not from the physical examination findings, but from the qualities of human nature observed. We shall go more thoroughly into these aspects of persons a little later, to see what groups or reaction types we may find.

One of our most vital qualities is the energy we possess, especially energy for doing useful work. The work record of patients is extremely important. How much can he do? How dependable is he? How consistently does he work? During the last World War the Germans did not use the word "psychoneurosis," but designated its counterpart as describing persons not overtly psychotic and with a *lowered threshold for useful work*.

Perhaps another way of saying this is that each person is endowed with a given amount of something we may call adaptability. It wears out, as life itself does. Those of our men and women between 18 and 45, or over, who have been entrenched in civilian life and have adapted to it, will have to readapt to the regimentation of military life, to heat, cold, high altitude, and to effects of the desert or the jungle, to say nothing of the enemy. When the war is over, they will be required to readapt again to a changed civilian world and do it with changed selves. The strain on adaptability is likely to result in some breakdowns that will require tolerance and understanding.

In World War I it was said that no new types of psychosis or neurosis were seen which were not found in civilian life. That was true and is essentially true today. Aviators who fly too much are said to become stale, bored, and irritable. Long-continued use of noisy mechanized equipment is a strain on attention and other functions as well. The very necessary and

*Read before the Regional Meeting of the American College of Physicians, Chicago, November 21, 1942

circumscribed regulations of naval men, especially while at sea, result in some breakdowns that may be peculiar to their work. The fact seems to be that anyone will break down if the stress, by virtue of its quality or degree, becomes great enough, and some persons will do so when the external stress is hardly perceptible. Gillespie¹ (Psychiatrist-in-Chief, for the Royal Air Force) has reported relatively little increase in the incidence of neuroses from the bombings in England unless there was predisposition. These latter conditions are a problem for induction boards which are doing a much better job in this war than they did in the last. Their work cannot be perfect because of latent subclinical tendencies in all of us.

Let us review briefly some of the types of neurosis likely to be encountered but first present a disorder that is common enough although not really a psychoneurosis.

Unstable States, or Reactions to Situations Often in life a person must make a difficult decision, or must face distressing facts and he may, as a result, become tense, tremorous, sleepless and emotional. Such conditions sometimes produce symptoms requiring the help of a physician. Patients not infrequently have headaches, or vomit, or ache under such stress. An opportunity to talk it over with an understanding friend, or clergyman, together with the relief of individual symptoms, is very helpful in such cases. Physicians occasionally make the mistake of giving the patient a list of serious diseases they have ruled out by their examinations, before concluding that matters are not serious. Quiet assurance and sound sleep are very therapeutic in such situations. Telling a patient that "it is all in your head" may lead to worse things. There are plenty of such mild disorders on every medical or surgical ward. Such patients appreciate reassurance and friendly advice; let us hope that the physician may not be so preoccupied with science that he fails to lend this human touch. These disorders have the same relation to psychiatry that the common cold has to infectious diseases, they are not very unusual, and often pass over quickly. An aviator flying too much, a soldier at the front too long, a sailor at sea too continuously, may show a little of such reactions. Such seemingly trivial and reversible disorders may have very strategic importance. An aviator may crash because of it. A gunner may miss his mark. A colonel or general may conceive or execute the wrong plan. Change, rest, relief, understanding are very therapeutic, although vigorous men may feel that they are indulging themselves when placed on such a regimen for even brief periods.

Now, let us turn to the disorders that are commonly called psychoneurosis, a word, I fear, used too glibly to dismiss an undesirable patient and to discharge a responsibility that does not really end when the diagnostic term is applied.

1. *Hysteria—Substitution Disorders* The disorder, hysteria, was first singled out by the ancients who believed that certain cries and distresses of women were in some way related to malpositions of the uterus, the word for uterus in Greek being *hysterios*. Not until the 17th century did the con-

cept change to include men, and then, of course, it became certain that it was not due to the uterus. The word "hysteria," however, lingers with us as a relic of false and ancient concepts. The term has wide use among laymen and refers to undue laughing or weeping, or emotional instability, for example, "crowd hysteria, hysterical with laughter, hysterical over bad news." A better term is *substitution disorder*, or *sublimation disorder*. Freud has contributed the chemical concept of sublimation, which is this: that emotions may not appear as such, but may appear instead as body disorders, or a deletion of body functions. There is a certain amount of *mimicry* about this. Butterflies mimic, so do rabbits, chameleons depend on mimicry for almost all of their protection. Why shouldn't man occasionally be so constituted that in the face of stress he unknowingly imitates disorders that he has seen, such as blindness, paralysis, aphonia, pain, gait disorders, forgetfulness, confusion, syncope, etc. These substitutions of body symptoms and personal behavior for the emotions growing out of stress are really *pseudo-symptoms* and are recoverable under the influence of suggestion, hypnosis, anesthesia, various types of narcotization, by establishing a penalty for retaining them, and rewarding by pleasure for giving them up. Faradic electricity judiciously used may help to accomplish this.

After the gross symptoms have been overcome, the patient's life needs to be organized so that unendurable stress is removed, and he is rewarded for remaining a useful citizen. All of these things must be done, not with the feeling that the patient is malingering, but in the spirit of kindness and firmness and hopefulness. To tell such a patient that there is nothing the matter with him is to fail before beginning.

2 *Invalidism, Irritable Weakness Syndrome*. Between the years 1860-1870, Beard and Van Deusen used the word, "neurasthenia," as a diagnostic term for patients disabled by weakness, irritability, and disappointment. Their patients were chiefly society women, bored by the round of futilities to which people subject themselves. The word itself means "weak nerves," and as such is clearly a misnomer. In certain forms of leprosy and neuropathies, and neuritides, there really are damaged and weak-functioning sensory and motor nerves which are definite structures carrying impulses between the periphery of the body and the central nervous system. Then, too, there are so many diseases and conditions that can make people weak, for example, Addison's disease, myasthenia gravis, incipient Parkinsonism, tuberculosis of the lungs, melancholia, too much work, no chance to rest, etc. The diagnosis "neurasthenia" is being used and spoken of less and less, and in some excellent clinics it is never made. But constitutional asthenia, or constitutional inadequacy, or the more accurate descriptive terms, *irritable weakness syndrome*, or *invalidism*, are more understandable as a real *energy defect*. Persons with energy defects, born into families of accomplishment, seldom have recourse to honest appraisal of themselves. They are obliged to explain their condition in terms of illness, which is socially approved,

and never in terms of the variation from the average in energy, which it really is This is illustrated by the history of "patient X" which follows

CASE REPORT

"X," aged 34, complained of tiredness, weakness, mild insomnia, and some indigestion for at least 12 years During childhood he had many colds and infections but none was serious In preparatory school he was never strong enough to take an active part in sports and sometimes a tutor was needed to help him with his studies He got on well with others His father is a successful manufacturer, a younger brother is a college teacher, an older sister is an active club woman, the mother of two children The family were disappointed when the patient was unable to go on with postgraduate studies—particularly the mother, quite a religious woman, who had hoped that her favorite son might enter a profession

The patient had been examined by several physicians The first told the family, "the physical examinations and laboratory tests are all negative, his trouble is *nothing but mental*" The family took offense at this Another physician found no body disease, but felt that the endocrines might be "out of line" and so prescribed extract of adrenal cortex, for a while it seemed to help, but not enough to satisfy the ambition of the family A third physician, noting that the patient maintained his weight with difficulty, wondered if he had received all of the vitamins he needed and accordingly these were prescribed The patient gained weight temporarily, but was unable to do more effective work These were only a few of the physicians who saw the patient Some advised less pampering and even intimated that he was "giving in to himself" These diagnoses were made by various physicians neurotic, neurasthenic, a plain case of nerves, chronic nervous exhaustion—apparently satisfying the physicians who made them, when in reality they should not, since "diagnosis" means "to know the disorder through and through" and merely attaching a word label is little better than classifying diseases by lottery Against their own wishes, and at the suggestion of a physician, the parents finally took the patient to a psychiatrist whose examination of the body, including the nervous system, likewise proved negative The family asked many questions and expressed the hope that the psychiatrist would find "X"'s trouble "merely nervous, and not mental" They were told that "X"'s body was in pretty good condition, but that *he as a person* was ill or disordered, that the disorder was of long standing and deep-seated—far more difficult to eradicate than some more striking conditions called mental The psychiatrist informed them that "X" was very honest and sincere about his disability, never "putting it on" for the sake of escaping responsibility He explained that if human beings were like machines or engines, cause and effect might be easily related, but, on the contrary, biologic evolution had created persons in whom cries of distress and evidences of disability were somewhat removed from the immediate apparent causes and might be symbols of something not quite obvious The psychiatrist further explained that such patients are often very intelligent, but have *energy defects* that interfere with family and personal ambition Charles Darwin, he told them, was such a person, accomplishing much with meager energies, although he was never quite at peace with himself or the world about him An effort was made by the psychiatrist to adjust the patient honestly to a program compatible with his real assets, "X" was disappointed in this, and he knew his family would be Later they sought the advice of a surgeon who focused on his indigestion, ignoring most of his other disabilities, and "X"'s appendix, not seriously diseased, was finally removed The last news of "X" reported him to be devoting a part of each day to oil painting, reasonably contented with his accomplishments, but ever mindful of how he had been "cheated out of success in life by bad health"

There is no place for "X" to fit into the duties and responsibilities of the active military forces, which are not therapeutic agencies. Should "X," by accident or otherwise, get into the armed forces, the ultimate cost to the government in providing for him runs into thousands of dollars, according to the records of World War I.

3 *Psychasthenia—Compulsive-Obsessive Neurosis* In 1903, Janet used the word psychasthenia as a diagnostic term for disorders characterized by "weak mind"—a literal translation of the word. By this, he did not mean feeble-mindedness, as the word might imply. He referred to those in whom indecision is a disability, and who are obsessively distressed and preoccupied with topics of an unusual nature, but with insight into their condition. Freud coined the more descriptive terms, compulsive-obsessive neurosis for such conditions. Individuals so affected are aware of the unreasonableness of their obsessions, and the absurdity of the compulsions, which are acts indulged in by the patient to bring relief for the obsessions. One of the commonest obsessions is a dread of dirt or filth. The compulsion indulged in to get relief is cleaning over and over again, or excessive hand washing, sometimes to the point of exhaustion. Other obsessions center in contamination fears, need for punctuality, for neatness and orderliness, "for saving one's soul," strange body feelings, fear of crowds, fear of diseases, etc. For relief from these obsessions, compulsions of meticulousness, scrupulosity, and frequent medical consultation and health precautions, or religious preoccupation, are often observed. Sometimes unusual rituals are followed. These patients adjust by an *uncontrolled and repetitious automaticity*. Alcoholic excesses are not infrequently on an obsessive-compulsive basis. Persons so disabled have unstable physiological equipment, and may vomit, have diarrhea, anorexia, and other symptoms, too, from the exhaustion created by repetition of compulsions.

The disorder occurs in two forms. One is insidious and has existed pretty much the whole life of the patient. This form is usually not responsive to therapy, and the most that can be expected, in our present state of knowledge, is to get the patient to adjust to some simple work that is not too demanding. The other form occurs in more or less circumscribed attacks. Such patients respond to treatment in much the same way that depressed or elated patients do, and tend to recover. Electroshock therapy may be of definite value with this group. Bilateral prefrontal lobotomy is said to be helpful.

4 *Anxiety Neurosis, or Anxiety States* These disorders occur when the patient feels that his life, or his integrity, is threatened. Many persons whose lives are menaced by serious disease do not develop a panic, or fear of death. On the other hand, persons may allow their thoughts and feelings to build up a conviction that death is imminent if relief is not obtained. *Pathological self-preservative reactions* form the basis of this disorder. Such attacks punctuate an otherwise tense existence which may last several months to several years. These disorders are not easily changed by sug-

psychoneurotics should be rejected for active military duty when recognized as such

SUMMARY

1 Absence of body disease is not a criterion for diagnosis of psychoneurosis. Psychoneuroses may have any of the body diseases that others have. They need the usual physical and laboratory examinations. The diagnosis is based on the positive way a particular kind of predisposed human nature adjusts. The relatively unpredisposed may develop a variety of symptoms resembling those of the psychoneurotic if under sufficient stress. These symptoms usually disappear quickly when the stress is relieved.

2 Substitution disorders (hysteria)* are based on *mimicry* found abundantly in plants and animals.

3 Invalidism (neurasthenia) is a way of adapting when there is a pronounced *energy defect* in a person goaded by ambition.

4 Compulsive-obsessive neurosis (psychasthenia) has its inception in a disposition to *uncontrolled and repetitious automaticity* of feelings and acts, which are also widespread among the animals of nature.

5 Anxiety neurosis is the adaptation of a person with *pathological self-preservative impulses and reactions*—the neurosis more intimately associated with the battlefield than any other.

6 (Hypochondriacal disorders) are forms of adaptation on the part of those with more or less personal disintegration in the nature of persistent delusions about the shape or functions of their bodies. These disorders tend to be chronic and are hardly to be distinguished from chronic psychotic states.

7 So-called (post-traumatic and post-concussion neuroses) are, with some exceptions, *affective disorders*, which may result from trauma. Shock effects in reverse, so to speak.

8 Many psychoneurotics respond to the various forms of therapy that are available. Treatment must be very individual. Despite their disability, many of them make a definite contribution to our culture, but are unfitted for active military service.

BIBLIOGRAPHY

- 1 GILLESPIE, R. D. Psychological effects of war on citizen and soldier, 1942, Norton, pp. 251.

* Misnomers are in parentheses.

THE TREATMENT OF FUNCTIONAL GASTRO- INTESTINAL DISTURBANCES OF NEURO- PSYCHIATRIC ORIGIN*

By JOSEPH C YASKIN, M D , *Philadelphia, Pennsylvania*

INTRODUCTION

THE gastrointestinal tract is particularly susceptible to functional disorders characterized by physiological abnormalities in the motor, secretory and sensory spheres, not due to any known primary structural or chemical causes, deficiency states or allergic disturbances, and traceable to neuro-psychiatric maladjustments. These cases are frequent in everybody's practice and are usually unsatisfactory from the standpoint of treatment. It is the purpose of this presentation to discuss treatment, but before doing so it is necessary to get some clear formulations of the rôle of the vegetative nervous system and more particularly some principles in general psychopathology of the psychoses and neuroses, and some special psychopathology of the psychoneuroses. Without these formulations no principles of treatment can be formed.

The Rôle of the Vegetative Nervous System The common denominator of all disorders of the gastrointestinal tract, either organic or functional, is the physiological disturbances in the various functions of the vegetative nervous system. The vegetative nervous system is the "great common path" in the various motor, secretory and sensory disturbances of this tract.

For practical purposes, the vegetative apparatus may be divided into three parts:

- 1 The autonomous structures comprised by the myenteric plexus of Auerbach and the submucous plexus of Meissner which, though autonomous, are markedly influenced by the two major divisions of the vegetative nervous system.

- 2 The two major divisions of the nervous system, the sympathetic (thoracolumbar) and the parasympathetic (craniosacral) systems. It is important to stress that both of these systems contain both efferent and afferent pathways.

- 3 The suprasegmental connections, also a two way system of which the *diencephalon* is probably the most important constituent. Experimental and clinical evidence suggests that the *diencephalon* plays a major rôle in regulating efferent impulses of both divisions of the vegetative nervous system. It is worth stressing that the *diencephalon* now is recognized as having a

* Presented in part at the Symposium of Functional Gastrointestinal Disturbances before the American College of Physicians, at the United States Naval Hospital in Philadelphia October 20, 1942.

From Department of Neurology and Psychiatry, Graduate School of Medicine, University of Pennsylvania.

marked influence upon the endocrine glands, metabolism and heat regulation, as well as receiving impulses from and sending them to the old and new brain and the neuraxis. Even more important is the fact that the region of the diencephalon is regarded as one of the major centers of emotions.

Little is known about the cortical representation of the efferent vegetative nervous system, but Fulton¹ states that such representation exists in the premotor area (Broadman Area VI).

The reader is referred to appropriate literature for a detailed discussion on the anatomy and physiology of the vegetative nervous system. Of particular interest to the clinician is the cause of pain arising from the viscera.

At one time it was thought that there were no sensory nerves in the viscera, especially in the gastrointestinal tract, and that pain was always a result of the involvement of the structures supplied by the somatic nerves, such as the parietal peritoneum.² Later it was agreed that pain occurs in disturbances of the gastrointestinal tract by overdilatation³ and overcontraction⁴ of hollow viscera and by stretching of the capsules of the solid organs. Still later Ross,⁵ Head,⁶ and MacKenzie⁷ evolved the concepts of viscerocutaneous, visceromotor, and viscerovisceral reflexes to explain the various painful phenomena originating in disease of the internal organs. More recently Leriche⁸ pointed out that the viscera have sense organs identical with those in the skin, but they are subjected only to intrinsic stimuli which, even if they reach consciousness, are not and cannot be interpreted in terms of other analytical data.

Recent experimental and clinical observations have led to the impression that the diencephalon plays a major rôle in the disturbance of the gastrointestinal tract both from physiological and emotional standpoints since the diencephalon is a relay station for fibers mediating a great many functions including the emotions.

When one bears in mind the physiology of the involuntary nervous system it becomes easier to understand why the gastrointestinal tract can become a prey to conditioned reflexes. This is particularly true early in life in relation to appetite, vomiting, constipation, diarrhea and other disturbances of the gastrointestinal tract. It is important to stress that these gastrointestinal disorders are not simple reflexes but rather, physiological reactions having their origin in complicated psychological situations.

General Psychopathology. The special psychopathology of the neuroses will be considered under the treatment of the neuroses. Here it is desired to state that every clinician, for purposes of treatment, should have some knowledge of the structure of personality, types of personality and reaction types.

Structure of Personality. Personality may be defined as the sum total of all reactions in a given individual. It includes the habitual patterns of behavior of the individual in terms of physical and mental activities and attitudes (Healy, Browner, and Bowers).⁹ A fundamental, empirical, but necessary concept of personality necessitates the division of the personality

into two parts unconscious and conscious. The unconscious monopolizes the greater part of personality. It has often been compared with the submerged part of an iceberg, the visible part representing the conscious. The unconscious is defined as a deep level of mental activity consisting of elements which never were conscious (collective unconscious of Jung¹⁰) and of elements previously in consciousness but forgotten, suppressed or repressed. *Suppression* is a purposive exclusion of ideas from the field of conscious attention. *Repression* is an unconscious exclusion of painful and unpleasant material from consciousness and from motor expression. Repression is directly or indirectly accomplished by that part of the personality which is concerned with the adaptation of the individual to the needs of reality. The unconscious is brought into consciousness only in dreams, abnormal states, and by special psychological technic. The conscious part of the personality is at all times markedly influenced by its larger unconscious part.

Types of Personality From a clinical standpoint personalities may be divided into the following groups: (a) average normal, (b) neurotic hysterical, hypochondriacal, oversensitive, compulsive-obsessive, (c) syntonoid (cycloid, extraverted), (d) schizoid (shut-in, introverted), (e) paranoid, (f) rigid, (g) constitutional psychopathic, (h) epileptic.

Reaction Types From the standpoint of psychopathology it is well to be familiar with the several reaction types. These include

(a) the *organic reaction type*, such as occurs in structural diseases of the brain due to vascular and degenerative changes, neoplasms, infections, intoxications, deficiency states, and characterized by predominantly intellectual difficulties,

(b) the *affective reaction type* comprising principally the cyclic manic-depressive reactions and involutional melancholia,

(c) *Schizophrenic reaction type* with the many bizarre modes of thinking, feeling and acting observed in various types of dementia praecox, and

(d) the *psychoneurotic reaction type* which will be discussed in detail later.

Functional gastrointestinal disturbances are observed with varying frequency in the various types of reactions. The etiological diagnosis depends, in a large measure, on evaluating the type of personality and reaction, and without such an evaluation treatment is unsatisfactory. It is important to emphasize that it is not the gastrointestinal disturbance that makes for the useful diagnosis, but the setting in which it occurs, that is, the evaluation of the associated clinical phenomena.

For practical purposes the treatment of the various gastrointestinal disturbances will be described first from the standpoint of their occurrence in the various psychotic reactions, and then in the psychoneurotic reactions.

TREATMENT OF THE FUNCTIONAL GASTROINTESTINAL DISTURBANCES IN PSYCHOTIC REACTIONS

Only the more frequent gastrointestinal disturbances will be touched upon in this presentation

Bitter Taste in Mouth This is almost a constant complaint in depressions, even in the so-called extramural depressions which are often misdiagnosed and treated for colitis (Yaskin¹¹)

Anorexia is a constant and prominent symptom in almost all depressions. Some depressed patients complain that they feel hungry but can not eat, that everything tastes alike or is tasteless. Many depressed patients have no appetite in the morning, but can tolerate or even enjoy a meal in the latter part of the day. With the onset of recovery the appetite for meals in the earlier part of the day improves.

Failure to eat is frequently observed in schizophrenia where it may be due to apathy, lack of interest, catatonic negativism or delusional states.

Anorexia is a common symptom in organic psychotic reactions.

Bulimia or excessive appetite is observed in some feeble-minded, in paretics and senile demented, and in some schizophrenics. The latter also evince a tendency to swallow all kinds of things, even their own excrement (coprophagia).

Picae, or peculiar cravings for food, are rare in psychoses.

Alternating anorexia and bulimia are often observed in early and borderline schizophrenia, sometimes accompanied by diet ceremonials. These phenomena usually represent morbid impulses (actions carried out without reflection and aimful willing), but may be due to delusional trends.

Pain, paresthesias and dysesthesias referable to the upper digestive tract, abdomen and rectal region are common in constitutional psychoses and require careful evaluation. They may occur as early and monosymptomatic manifestations in dementia precox and especially in involution melancholia. Indeed, in the latter disease, they may receive considerable attention from the organically minded internist who fails to observe the associated personality disturbances. Many useless investigations and operations are performed before the patient shows the more fundamental evidences of agitated depression and anxiety.

Salivary, gastric, biliary, and pancreatic secretions show some changes in the various psychoses.¹²

Cardiospasm is rare in psychoses, but vague complaints of difficulty in swallowing are fairly common early manifestations of involution melancholia.

Gastric and intestinal *motility* is disturbed in most of the psychoses.¹³

Constipation is a common manifestation of most psychoses, but especially the depressions. Fecal impactions are frequently found in psychotics. The depressed patient fails to move his bowels because of atony, psychomotor retardation or delusional states. In the schizophrenic retention of the feces

is observed in catatonic negativism, in delusional states, and most commonly due to apathy and inattention

Vomiting is rarely seen in schizophrenia but is not uncommon in the tubefed depressed patient who makes every effort to terminate his life

Hypochondriacal and nihilistic delusions such as those in which the patient is convinced that his bowels are obstructed and that the stomach is cancerous, are most common in involution melancholia, but may be seen in the early stages of dementia precox. The psychopathology of these delusions is interesting

In reviewing the various gastrointestinal disturbances encountered in the psychoses one readily observes that the same manifestations may occur in the several types of reactions. It seems that the psychotic disturbances are reflected in changes of secretion, motility and sensation at the vegetative-visceral level, but in addition, misinterpretations and elaborations at the psychic level occur, resulting in hallucinatory and delusional formations. The early recognition of the underlying etiological psychotic process is of more than academic importance. With recent advances in the treatment of the psychoses, especially manic-depressive and involution melancholia, in which gastrointestinal complaints are early and prominent symptoms, a timely diagnosis means not only shortening the time of suffering and prevention of suicide, but effective immediate treatment. In schizophrenia the advances in treatment are less spectacular, but there are those who believe that early insulin shock therapy, plus psychotherapy, result in some recoveries, in many arrests of the disease, and in some improvement.

In turning our attention to functional gastrointestinal disturbances, as observed in the neuroses and psychoneuroses, we must utilize an entirely different approach if we are to be therapeutically successful.

TREATMENT OF THE FUNCTIONAL GASTROINTESTINAL DISTURBANCES IN PSYCHONEUROTIC REACTIONS

Every experienced internist is aware that the gastrointestinal disturbances occurring in the neuroses do not differ widely from other disturbances in the same disease. Furthermore, it is generally recognized that the treatment of the neuroses is often difficult and frequently unsatisfactory in the hands of the general practitioner, internist and others not specifically interested in neuropsychiatry. The reasons for these difficulties arise from failure to appreciate the importance of a number of factors, some of which it is my purpose to discuss. These factors include

- 1 Failure to possess a minimum knowledge of the psychopathology of the neuroses

- 2 Faulty attitude of the physician to the problems of diagnosis and treatment

- 3 Lack of a thorough knowledge of a few principles in therapy.

Some Basic Principles of the Psychopathology of the Neuroses The psychoneuroses and neuroses may be defined as conditions characterized by a variety of subjective complaints without any primary structural or chemical causes to account for their existence and generally traceable to some disturbance in the psychological processes of the individual. In the psychoneuroses the causative factors are traceable to occurrences and phantasies of early life with reactions to these incidents in the form of personality traits. In the neuroses the causative factors are traceable to occurrences or situations in the recent past or immediate present. In this presentation the terms "neuroses and psychoneuroses" will be referred to as "neuroses."

There is no gross or microscopic morbid anatomy or chemical aberrations to guide the physician in the diagnosis and therapy of the neuroses. Yet neuroses, like other natural phenomena, must have a beginning, an evolution and some reason for the various manifestations. This is to be found in certain psychopathological formulations, not all of which stand the tests of scientific criteria. Thus the concept of "personality" itself is, for the most part, a philosophic abstraction, but one without which treatment of the neuroses is hardly possible. The personality as previously stated is the sum total of all reactions experienced by an individual. From the standpoint of the neuroses the most important aspect of the personality is the *emotional* (affective) reaction. These emotional reactions may have their origin in situations of which the patient is perfectly aware (in the conscious) or (in the unconscious) in occurrences or phantasies of the past of which he is totally unaware. The existence of the unconscious has not been proved but, at present, it is a necessary hypothesis in the management of the neuroses. The unconscious activities of the personality are comparable to the activities of most of the thoracic and abdominal viscera of which we are not normally aware but which, nevertheless, exert a determining influence on our very lives. It is only when the viscera become disturbed that we become *aware* of them by reason of symbols which we call symptoms. Symptoms in organic medicine are often clever disguises, as edema in Bright's disease, glycosuria in pancreatic disease, etc. It has taken thousands of years to correlate the bizarre symbols with their true causes. This tendency for nature to disguise and symbolize is even more marked in psychopathology and makes the subject at times very complex, but, just as in organic medicine, there is always a chain of events to account for the occurrence of the various phenomena. Most of us can understand the occurrence of tachycardia, vomiting, diarrhea or fainting as an *immediate* result of some great emotional shock as easily as we understand the vomiting in obstruction of the gastrointestinal tract or the tachycardia in the failing heart. Some may doubt that insomnia, abnormal fatigability and irritability, phobias and many visceral disturbances are entirely due to emotional disturbances which occurred years before the development of the symptoms, although none of us *at present* questions that tabes and other marked changes in the various organs had their origin in a humble small cutaneous lesion called a

diagnosis of psychoneuroses and neuroses implies the absence of any primary structural or chemical disease, the existence, in the majority of cases, of a certain constitutional make-up (the predisposing causes), the occurrence of precipitating or exciting causes, and the formation of symptoms which may be in the psychic or in the physiological sphere, or in both. The constitutional factors may be inherited or acquired. In the "neurotic personality" the neurosis is "built into the character" and is characterized by manifestations intermediate between normal character traits and neurotic symptoms (Jones¹⁹). Symptom formation results from the action of some exciting cause which may be an injury, infection, a chemical disturbance, or some emotional stress. The symptoms may continue long after the exciting cause ceases to operate, and thus represent release phenomena of the neurotic traits of the previously apparently well integrated personality. These symptoms include either frank anxiety states or symptoms tending to avoid anxiety such as conversion, compulsive-obsessive neurasthenic reactions²⁰. These symptoms vary in severity from a slight headache, increased fatigability and irritability, to devastating visceral disturbances, intractable insomnia with marked agitation, and alarming loss of weight. The clinical manifestations frequently overshadow completely the primary constitutional factors or the immediate precipitating mechanisms.

Anxiety is the central symptom of nearly all the neuroses and psychoneuroses and is of fundamental importance in the management of all neuroses. Anxiety may be defined as one of the clinically important major emotions recognized introspectively as an unpleasant feeling, accompanied by fear without any, or without adequate cause, and manifested objectively by normal changes in the neuromuscular, autonomic, and secretory functions (emotional expressions). All neurotic symptoms are derived from anxiety arising in the conscious or unconscious parts of the personality. These symptoms include frank anxiety or conversions and substitutions for anxiety reflected in disturbances in the physiological or emotional spheres.

There are many *mechanisms* by which anxiety is converted into symptoms and those interested will search for these in publications on psychopathology⁹. Here it is worth stressing the rôle that *hostility* plays in a good many neurotic conditions. Anxiety gives rise to hostility, which in turn generates more anxiety and thus a vicious circle is established. Both the anxiety and hostility are experiences of which the patient is not at all or only poorly aware. The existence of both anxiety and hostility helps to explain the reasons why "the neurotic person may at the same time be driven imperatively toward dominating everyone, toward complying with others and imposing his will on them, toward detachment from people and craving for their affection. It is these utterly insoluble conflicts which are most often the dynamic center of the neuroses. The two attempts which most frequently clash are the striving for affection and the striving for power" (Horney²¹).

chancere It is a fact, nevertheless, that many neurotic symptoms are prolongations of early emotional states which remain dormant in the unconscious part of our personalities until some exciting cause activates them

The concept of the neuroses as a distinct clinical entity is necessary for diagnosis and especially for successful treatment In actual practice, however, it is frequently difficult to distinguish between what is "neurotic" and what is "organic" This is due to the fact that every disease must be considered as having both a somatic and a psychic component The two components are indivisible and should be evaluated in their relation to etiology and to the total situation (Weisenberg, Yaskin, and Pleasants¹⁴) Whether the disease arises as a result of structural changes in the soma, of abnormal chemisms, or of emotional conflicts or abnormal psychic tensions, a change of affect of the individual (the subjective phase) and corresponding changes in the neuromuscular, autonomic, and secretory functions (objective evidences-emotional expression) takes place As stated previously the principal relay station for emotional components of diseases appears to be in the diencephalon It is responsible for the correlation of psychic and somatic disorders, has a regulating influence upon both of the major divisions of the vegetative nervous system and indirectly upon most of the endocrine glands, upon metabolism, and heat regulation It also receives impulses from, and sends impulses to, the old and new brain and the neuraxis In primary somatic disease this center receives abnormal impulses and registers them in the viscera in the form of emotions, especially in the abdomen, the "sounding boards of emotions" (James¹⁵) In disorders of the general chemism the center may be affected directly or centripetally via the vegetative nervous system In states of emotional conflict and abnormal tension this center may be influenced from the cerebral cortex and then set up impulses responsible for secondary changes in function and in structure of the viscera (Alvarez,¹⁶ Moschowitz,¹⁷ Weiss¹⁸) A consideration of these factors requires as criteria for the diagnosis of a neurosis not only the absence of any primary physical or chemical changes, but more particularly the finding of satisfactory psychological causes to account for the clinical manifestations

The above two criteria for the diagnosis of minor psychoses make such a diagnosis very difficult The coexistence of organic gastrointestinal disease and neurotic symptoms is well known, and their etiological relationship is often difficult to evaluate Even with very painstaking investigation, organic disease may not be correctly diagnosed and the cases managed as neuroses The causes for such errors have been reviewed elsewhere¹⁴ Even more difficult, however, is the finding of adequate psychogenic causes without which therapy is often futile The chief reason for this difficulty is that our present psychopathology is definitely unsatisfactory and, when subjected to scientific criteria of proof, is not completely convincing even to the most sympathetic observer with the objective method of thinking However, there is general agreement that for therapeutic purposes the

It is necessary to emphasize two other factors

(a) *A given group of symptoms (such as gastrointestinal or cardiac) is only a conspicuous part of the total neurosis* The symptoms can rarely be successfully treated without evaluating the total situation

Just what determines the occurrence of disturbed function in some organs and not in others is not definitely known The choice of the organ involved may be traceable to one or more of the following factors

(1) An inherited structural or functional inferiority of some organ (Adler ²²)

(2) Acquired constitutional traits through early inhibitions and frustrations, especially in the psychosexual spheres, possibly the formation of complicated conditioned reflexes, and

(3) Incidental but frequently precipitating causes which often act through auto- and hetero-suggestion and other psychic mechanisms in a manner entirely unknown to the patient, but having a definite relation to some experience or phantasy in earlier life

(b) The various symptoms and their special etiology, psychopathology, prognosis and treatment differ somewhat in the several types of neuroses ²³ These types include anxiety neurosis, conversion hysteria, anxiety hysteria, neurasthenia and compulsive-obsessive reactions The description of these various types, as well as the borderline conditions such as gastric ulcer and ulcerative colitis will be more conveniently discussed under the heading of treatment Here it may be stated and emphasized that the various functional gastrointestinal disturbances may occur in any of the five types mentioned, and that their etiologic, psychopathologic and therapeutic factors differ widely Psychotherapy concerns itself not so much with "the symptoms" anorexia, esophagospasm, cardiospasm, pylorospasm, bulimia, painful affections, pyrosis, globus hystericus, mucous colitis, irritable bowel, vomiting, diarrhea, constipation, hiccups, aerophagia, etc, as with the *emotional reaction* responsible for the physiological disorders or abnormal personality attitudes

The Attitude of the Physician to the Problem of Diagnosis and Treatment The management of the neuroses imposes upon the modern scientifically minded physician many hardships and even punishments He was nurtured and assumes himself living in an atmosphere of precision with controls in diagnosis and treatment This scientific atmosphere does not yet exist in the psychopathology or treatment of the neuroses In the management of the neuroses he must use an entirely different technic If he is, and he should be, of a critical type of mind he finds great difficulty in dissociating himself from his "organic" leanings despite all his efforts to the contrary But even if he is willing to accept the teachings of psychopathology and has a working knowledge of this subject, he is confronted

with the most difficult aspect of the problem, namely the *time element necessary for examination and treatment*. The management of most of the common neuroses requires much time, which those practicing medicine cannot spare. Lastly, it is necessary to emphasize that some physicians are constitutionally unfit to manage neuroses, just as some physicians cannot be good surgeons, obstetricians, or pediatricians.

Some Principles in Treatment There are many schools of thought concerning the treatment of the neuroses. There are still those who attribute the neuroses to *organic* conditions and accordingly stress the importance of the removal of foci of infection, prolonged physical rest, tonic medication, physical therapy, and change of environment. Some hold that persuasion and rationalization will cure most neuroses. Others depend on suggestion (including hypnosis), and still others on the so-called individual psychology, analytical psychology, group analysis and Freudian analysis or some of its several modifications. Some of the systems of treatment are totally unsuitable except for those who devote their time exclusively to psychotherapy. Most neuropsychiatrists use one system with their individual modifications.

The suggestions for treatment here presented may be utilized by those not specializing in neuropsychiatry. Such treatment will take care of some of the common neuroses such as anxiety neurosis, conversion hysteria, and some cases of anxiety hysteria. Many cases of anxiety hysteria and nearly all obsessive-compulsive reactions should be treated by qualified neuropsychiatrists.

As in other branches of medicine it is better to know and employ a *few procedures well* rather than to resort to many procedures in a haphazard fashion. Possibly in no branch of medicine is treatment less understood or systematized. Haphazard treatment not only decreases the benefit to the patient but does not improve the physician's acumen. On the other hand, if the physician becomes skilled in the employment of a few procedures he will eventually acquire new ones and will finally become a good therapist.

For purposes of treatment we may compare a neurosis with some acute infectious process, such as pneumonia. In the latter disease the fundamental process is the systemic infection with pathological lesions predominantly in the lungs and accompanied by annoying symptoms such as pain, cough, and an unpleasant systemic reaction. In the neuroses a similar state exists. The primary process, however, is in the realm of emotions and only mild secondary physical disturbances accompany the state. The basic principle in the treatment of pneumonia is to overcome the underlying infection, and at the same time, the annoying symptoms are allayed by various means. In the treatment of the neuroses exactly the same principles are followed. To the psychotherapist the emotional disturbances, conscious or otherwise, have just as much significance as does the infection to the physician treating the pneumonia. The therapist must have this approach if he is to be successful with his patients. If the therapist has

such an attitude he is not likely to state to the patient at the conclusion of the physical and laboratory investigations "There is nothing the matter with you I can find nothing wrong with you Don't be crazy, forget about it and snap out of it" He should rather say to himself "It is now my business to determine the emotional factors which produced the soil, and facts in the evolution of the tension and disguises reflected by the patient's complaints"

The treatment varies with the several types of neuroses The discussion will be considered under the following headings

- A Psychotherapy applicable to most common neuroses
- B Treatment of symptoms
- C Treatment of anxiety neurosis
- D Treatment of conversion hysteria
- E Treatment of anxiety hysteria
- F Treatment of compulsive-obsessive reaction
- G Treatment of borderline conditions—peptic ulcer and ulcerative colitis
- H Treatment of organic gastrointestinal disease, complicated by neurosis

A Psychotherapy This is useful in the treatment of all neuroses and neurotic manifestations complicating physical disease, but is especially useful in anxiety hysteria (sometimes called neurasthenia, anxiety state or nervous exhaustion)

Psychotherapy is a procedure which aims to correct the underlying psychopathological difficulties, as well as the various symptoms of which the patient complains It is a psychological device used to change the attitude of the patient toward himself, toward his physical and mental processes, and toward his environment It is an attempt to reevaluate his various life problems in relation to his various symptoms in the light of intellectual but, especially, emotional experiences For descriptive purposes psychotherapy is divisible into several artificial stages

1 *Rapport* This is a relationship between physician and patient whereby the latter gains confidence in and respect for the therapist, and at least a desire to cooperate despite preconceived notions of the origin of his symptoms Rapport is indispensable for successful treatment and is probably the most important step in the treatment To attain the attitude of a satisfactory rapport the patient must feel that the physician not only sympathizes with him, but also that he has a clear formulation of his case and has the ability to help him To justify to the patient's expectations the physician must not be too hasty in arriving at conclusions but once the formulation is made he must remain firm in his statements, betray no doubts or indecisions, and above all be frank and truthful

The establishment of rapport begins with the taking of the history. The history should be complete and should be recorded at once. The patient should be given ample time to tell his story even if repeated visits are necessary. The physical examination should be complete. Necessary laboratory procedures should be made, and at times some special examinations such as roentgen-ray of the skull, electrocardiograms or gastrointestinal roentgen-rays should be made even though in the clinician's judgment such examinations are not necessary. Once the physical investigations are completed and found negative, *reexaminations are most inadvisable* since they unsettle the patient.

At this point the physician is in a position to inform the patient that his symptoms are not due to physical causes but emphasize that his complaints are undoubtedly due to other factors which are in need of treatment. Without being specific the average patient will understand the statement that just as physical causes result in emotional disturbances so emotional disturbances may cause physical derangements, and that irrespective of origin, the patient's disability requires medical treatment. One may add that the human mind is at least as complicated and intricate as the human body and that disturbances of either are problems for treatment. Some common sense examples of effects of fear and the other major emotions may be given at this point. It may also be necessary to state that absence of physical causes does not mean that the patient is insane or that he "imagines" his symptoms. Above all at this point the patient must be assured that he will get well although progress be imperceptible at first and that he will have to help the physician actively in the treatment.

The patient is next given the general statement that his individual symptoms are undoubtedly a source of unhappiness and will receive palliative treatment just as cough and pain in pneumonia would be treated. He should be made to understand that the success of the treatment depends upon tracing and correcting unusual attitudes and reactions of his personality of which the presenting symptoms and nervous tension are conspicuous manifestations.

2 Ventilation or acration This consists in bringing into conscious attention in specific detail unwholesome attitudes and reactions which are usually associated with irritating memories. Some material is usually elicited in a detailed initial history. More information will be given by the patient when he is permitted to talk freely in direct interviews. Often, however, it is necessary to use the free association method. It should be stressed that ventilation is not merely a diagnostic procedure. Its goal is to give the patient the opportunity to discharge and bring out in the open all possible life experiences and phantasies which might have been causing him difficulties either consciously or unconsciously.

Ventilation should be supplemented by procuring from outside sources all possible information regarding the experiences and reactions of the patient, and the actual environmental factors in which he lives.

3 *Desensitization* This consists in removing by intellectual discussion the unpleasant emotional tone attached to the irritating memories. The patient is encouraged to face openly the unpleasant experiences and memories of the past. To accomplish this the material must be brought into consciousness repeatedly. This is done either by direct interview or by the free association method. In the course of time there is usually a better objective understanding by the patient and, what is more important, the emotion loses its unpleasant "sting."

The physician should guide the patient in this phase of the treatment. An element of suggestion is neither avoidable nor undesirable provided the therapist does not abuse it. It is necessary that the desensitization should be gradual to avoid severe "shock" reaction, and prevent undue wounding of sensitivity and pride and slowly build up tolerance to unpleasant emotional realizations.

It is best to leave most patients with some formulation at the end of each treatment period.

4 *Retraining, reeducation and stabilization* This consists in guiding the patient to react more or less *automatically* in a symptomless, efficient and wholesome manner to various stresses in life. The responses to be more or less automatic must be free from unpleasant emotional tone which is accomplished by desensitization and must be learned, at least in the adult, by persistent conscious effort. As a necessary part of lasting successful retraining and reeducation the patient should be guided in formulating an economic, social and recreational plan which will vary markedly with the individual patient.

5 *Psychotherapy of family* It is often necessary to desensitize the various members of the family to the patient's illness and reeducate them into new modes of response toward each other and toward the patient.

6 *Compromise formation* The neurotic situation is often complicated by various stresses such as marital, economic or social problems which cannot be eliminated. The patient should be made to face the facts of the situation and work out some compromise for himself.

B Treatment of Symptoms In addition to gastrointestinal the more common and important symptoms of neuroses consist of general tension and anxiety, abnormal fatigability, insomnia, fears of death and insanity, complaints referable to the heart, and pains in various parts of the body. Theoretically symptoms, as such, should be ignored since they are merely manifestations of the underlying psychopathological process at which our main therapeutic attack is directed. Practically, it is often necessary to pay wholesome attention to the complaints.

Certain general principles in the treatment of symptoms should be observed. They are

(1) *Avoid unnecessary surgery* Focal infections play no role in the fundamental psychopathology of neurosis. For example, the removal of

doubtfully diseased tonsils should not be preceded by the promise that it will cure the neurotic manifestations. The removal of a large fibroid tumor should be preceded by statement that it will probably have no effect on the lasting gastrointestinal or other symptoms such as the fear of insanity, abnormal fatigability, and daily headache which have existed for 10 years.

(2) *Explain to the patient the evolution of the symptoms from faulty emotional reactions.* Do not tell him they are imaginary and that he should forget them. If circumstances permit, some explanation should be given of how anxiety may give rise to such physiological disturbances as tachycardia, vomiting, crampy pain, frequent mucous stools, etc. Tell him that medication, dietetic treatment, etc., are given only for the *secondary* manifestations and will not affect the basic disturbance. For the same reason *avoid ritualistic procedures* (including diet ceremonies) which tend further to complicate the already muddled existence of the patient.

(3) *Physiologic and psychologic symptoms should not be neglected* while the patient is under psychotherapy. It is true that as ventilation and desensitization reach a satisfactory level the symptoms will become less severe, but it is equally true that

(a) A markedly tense, anxious and restless patient will be benefited by removal from home to a hospital or sanatorium.

(b) General weakness and easy fatigability will be allayed by rest in bed from a day or two to two to four weeks. The fatigue should not be ascribed to actual overwork which by itself is rarely a cause of neurosis.

(c) Malnutrition requires proper alimentation, vitamins, tonics, etc. Gastrointestinal symptoms, though secondary, should be corrected by a suitable dietary regimen until the patient "finds himself." The use of alcohol, tobacco, and coffee should be considered.

(d) Insomnia should be treated with great care. *The psychoneurotic, unlike the manic-depressive individual, is apt to become a drug addict.* Nevertheless, in the early acute stages of a neurosis or of a recurrence of a neurosis, somnifacients at night and sedatives through the day are almost indispensable. As the tension disappears it will be easy in the majority of cases to eliminate the use of somnifacients and sedatives.

(e) Phobic and panicky attacks are best not treated by medication as this often interferes with psychotherapy. In some cases phobic symptoms actually can be cured by deconditioning and training, and at least one should not encourage fear reactions by giving them false crutches.

Before proceeding with discussion of the several types of psychoneuroses it is wise to indicate that from a psychopathological standpoint the underlying process may vary in *depth* and *extensity*. Thus, the state characterized by functional manifestations having their origin in situations in the immediate present or recent past and occurring in an otherwise well integrated individual is called a *neurosis*. When the *predisposing* causes are due to deep-seated personality difficulties the resultant condition is a *psychoneurosis*,

even though the exciting cause may be quite superficial. It is obvious that the more extensive the psychopathological distortion the more difficult will be the treatment. As in other branches of medicine, types are not always pure and mixtures are common.

C Treatment of Anxiety Neurosis By anxiety neurosis is meant an episodic occurrence of anxiety, accompanied by somatic symptoms, especially palpitation, trembling, sweating and general weakness, less frequently by vomiting and diarrhea, and by complete or nearly complete freedom from symptoms between attacks. The precipitating causes of anxiety neurosis are in the immediate present or in the recent past. The most common causes are unsatisfactory sexual experiences (such as coitus interruptus, sudden cessation of masturbation in late adolescence, etc.) or threats to economic or social security.

The vomiting of children in the early grades which occurs only on school days belongs to this type of reaction. Similarly diarrhea of students at examination periods, and the vomiting of those who fear illegitimate pregnancy, reflect the abnormalities of an anxiety neurosis.

The *treatment of anxiety neurosis* is usually satisfactory. The cause should be removed if this is at all possible. When the cause cannot be removed, the patient must develop substitutive activities such as new interests and recreational outlets, and in some cases compromise formations.

D Treatment of Conversion Hysteria Conversion hysteria is characterized by the presence of motor, sensory, visceral, and episodic phenomena (conversion symptoms) accompanied by little or no anxiety, not due to any primary physical or biochemical abnormality and traceable to some definite psychogenic cause.

Conversion hysteria occurs in individuals who are hypersuggestible and emotionally immature. In conversion hysteria there is always a *motive* either to obtain something otherwise unobtainable or to escape a situation which is unbearable. The ordinary traumatic neurosis has a large element of conversion hysteria, the motive for which is not difficult to find.

Other precipitating causes in this group of cases are usually not difficult to find, and are often related chiefly to marital difficulties, death in the family, to a feeling of economic or social insecurity, or to many other life situations.

The most common gastrointestinal symptoms encountered in conversion hysteria include globus hystericus, vomiting, aerophagia, hiccups and diarrhea but nearly any other physiological disturbance may be present.

Suggestion in some form is probably the first method of treatment to be employed in these cases. Attempts at compromise formation in marital and economic difficulties also require and deserve considerable attention. The end result in these cases is usually good provided the cause can be removed or the patient be induced to make some compromise.

E Treatment of Anxiety Hysteria (neurasthenia, anxiety state, nervous exhaustion) Anxiety hysteria is characterized by a variety of somatic

complaints not due to primary physical or biochemical causes, accompanied by diffuse anxiety or by phobic phenomena, and traceable to psychogenic, often unconscious, causes

Constituting over 60 per cent of all cases, anxiety hysteria is the commonest of the psychoneuroses and neuroses. It is variously designated as neurasthenia, anxiety state, or nervous exhaustion. Anxiety hysteria occurs in the oversensitive and hypochondriac type of neurotics. It is the most common psychoneurosis encountered in gastrointestinal practice and constitutes a considerable percentage of this practice. It is in anxiety hysteria that one encounters esophagospasm, cardiospasm, pylorospasm, mucous colitis, pyrosis, aerophagia, alternating constipation and diarrhea, and a variety of painful reactions. Apprehension is a constant companion of these symptoms.

The predisposing causes are deep seated in the personality, frequently related to the early psychosexual life, whereas the precipitating causes are related to the numerous life situations.

The treatment of anxiety hysteria is often difficult. Some cases can be treated by the methods outlined in this presentation but not a few require intense psychotherapy in the form of analysis.

F Treatment of Compulsive-Obsessive Reactions (psychasthenia)
Compulsive-obsessive reactions are characterized by the existence of irrepressible thoughts and irresistible impulses designed to avoid anxiety, by the patient's recognition of the absurdity of these thoughts and impulses and by the appearance of anxiety when the patient attempts to "disobey" the thoughts and impulses. The personality history shows a very definite neuropathic trend. This becomes more evident when even a partial analysis is attempted. By this method neurotic traits are found to have existed since childhood, but were thoroughly integrated in the personality make-up and did not produce disability symptoms until somewhat later in life. The precipitating causes can only be ascertained by a partial analysis and then are to be found largely in the psychosexual sphere. It is in this form of psychoneurosis that any treatment short of partial analysis is of little value.

Gastrointestinal disturbances are rare in the compulsive-obsessive reactions.

G Treatment of Borderline Conditions, Peptic Ulcer and Ulcerative Colitis
The rôle of emotional factors in peptic ulcer and ulcerative colitis remains a moot question. There can be no doubt that emotional disturbances *aggravate* existing lesions and there is good reason to believe that emotional strain may reactivate quiescent lesions.

It would seem that peptic ulcers occur in individuals whose makeup may be characterized by rigidity, over-conscientiousness, and even intolerance, in individuals who are overly honest and meticulous, usually dynamic and often aggressive but who do not develop compulsive-obsessive tendencies. One may suggest that the prolonged nervous tension and anxiety could result in disturbances of secretion and motility leading to peptic ulcer, but proof is

lacking that such is the mechanism. However, there is some evidence that cerebral lesions, principally in the diencephalon, are associated in the ulcerations in the gastrointestinal tract²⁴

Based on personal observation of a few cases and on a study of the literature, I am unable to formulate a type of personality or definite psychological mechanisms that could be considered as primary causes of *ulcerative colitis*

H Treatment of Organic Gastrointestinal Disorders Complicated by Neuroses The problem of neurotic manifestations complicating organic gastrointestinal diseases is not vastly different from similar complications in other organic diseases. Such neurotic manifestations may *antedate* the organic disorders and indeed may act as precipitating or aggravating factors in such diseases as peptic ulcer or ulcerative colitis. On the other hand, the organic disorders may bring out *latent* neurotic traits which may interfere with recovery and convalescence and indeed may last long after the organic lesion has been arrested or eradicated. The neurotic manifestations may be quite frank or may be masked. In the latter event the suspicion of the complicating neurosis is aroused when the patient's attitude does not correspond to evidences of improvement of the physical disease.

It is in these cases of organic disease complicated by neurotic complications that the psychotherapist must exercise utmost caution, acumen, and judgment. In the first place he must be enough of a clinician to evaluate the *organic phases* in relation to the total situation. He must next be able to evaluate the *personality pattern* harboring both the organic and neurotic factors. He must then bring out and evaluate the *psychogenic factors* which may be responsible for the neurotic manifestations. The consideration of the psychogenic factors is complicated by the following situations:

(a) In not a few organic cases *superficial inquiry* fails to disclose any emotional difficulties. Indeed, single or brief interviews may lead to the erroneous conclusion that the individual has no emotional problems. This may be due to the patient's own ignorance of his situation or to his unwillingness in the presence of organic disease to establish a rapport with the psychotherapist necessary for psychological investigation. The psychotherapist himself may be influenced by the organic factors to such an extent that his usual persistence may be discouraged.

(b) The discovery of psychogenic factors of remote or recent past, or even immediate present, need not lead to the conclusion that such factors are responsible for the neurotic manifestations. Such fallacious reasoning is harmful enough in the management of the uncomplicated psychoneuroses but is therapeutically disastrous when practiced in cases with organic disease and leads to considerable resistance and actual unhappiness on the part of the patient. It is not the many and varied unpleasant incidents and situations which occur in many individuals' lives which determine the formation of

neurotic symptoms but "the patient's ability to adjust to such situations, especially his reactions to them, the degree of pent-up anxiety, the nature and seriousness of his conflicts, that must be evaluated" ²⁵

(c) After a careful evaluation of significant psychogenic factors, desensitization and new adjustments should be made gradually and with much caution. The neurotic with organic disease is even less willing to abandon his personality tendencies than is the uncomplicated neurotic. It is in these cases that "compromise formations" are most needed and difficult to achieve. It is as often as much a problem for the internist as for the psychiatrist and indeed the psychiatrically minded and *trained* internist can often do it better than the average psychiatrist.

SUMMARY

The so-called functional disorders of the gastrointestinal tract are disturbances in motility, secretion and sensation of this tract caused by dysfunction of the vegetative nervous system in its various ramifications. Such disorders may be due to a number of causes among which psychological factors are common and important. The diencephalon probably plays a major rôle in the conversion of psychic disturbance into gastrointestinal manifestations by reason of its being a center for several related functions.

In the psychotic reactions, gastrointestinal symptoms are common. Early, especially in schizophrenia and involution melancholia, the gastrointestinal manifestations may mask the fundamental disease process. Mild psychotic reactions, especially depressions, may go unrecognized by reason of the preponderance of the gastrointestinal symptoms. The treatment should be directed to the underlying psychotic condition.

In the psychoneuroses and neuroses the gastrointestinal manifestations may be the conspicuous manifestations of the total neurosis. To treat these cases the physician must have a minimal knowledge of psychopathology with some formulations regarding the structure of personality, various types of reactions, the nature of anxiety and its various modifications, and learn to understand his patient in terms of symbolizations and tensions. He must be prepared to devote considerable time to enable him to have a clear formulation of the problems of the individual patient.

The success of treatment, in the majority of cases, depends upon some evaluation of the underlying psychopathology and a thorough knowledge of a few therapeutic procedures applicable to most psychoneuroses and neuroses and special procedures in the treatment of some types of neuroses and symptoms.

The several types of neuroses and psychoneuroses vary in their symptomatology, etiology, psychopathology and treatment.

What not to do in the treatment of the psychoneuroses and neuroses is also important.

BIBLIOGRAPHY

- 1 FUITON, JOHN F Physiology of the nervous system, Oxford University Press, New York, 1938, page 469 et seq
- 2 LEVINSKY, K G Über die Sensibilität der Bauchhöhle und über lokale und allgemeine Anästhesia bei Bruch- und Bauchoperationen, Zentralbl f Chir, 1901, LVIII, 209
- 3 HILAST, A F On the sensibility of the alimentary canal in health and disease, Lancet, 1911, I, 1051-1056, 1119-1124, 1187-1193
- 4 RYLE, J A Visceral pain and referred pain, Lancet, 1926, I, 895 The clinical study of pain with special reference to the pains of visceral disease, Brit Med Jr, 1928, I, 537
- 5 ROSS, J On the segmental distribution of sensory disorders, Brain, 1887, X, 333
- 6 HENRY, H On disturbances of sensation with especial reference to the pain of visceral disease, Brain, 1893, XVI, 1
- 7 MACFARLANE, J Some points bearing on the association of sensory disorders and visceral disease, Brain, 1893, XVI, 321 Symptoms and their interpretation, 1912, Shaw and Sons, London Angina pectoris, 1923, Oxford Medical Press, London
- 8 LERICHE, RENE The surgery of pain (translated by A Young), 1939, Williams and Wilkins, Baltimore
- 9 HEALY, W BROWN, A F, and BOWERS, A M The structure and meaning of psychoanalysis, 1930, Knopf, New York
- 10 JUNG, C G Psychology of the unconscious, 1916, Moffett, New York
- 11 YASKIN, J C The feeling of unreality as a differential symptom of mild depression, Arch Neurol and Psychiat, 1935, LVIII, 368
- 12 DUNBAR, H F Emotions and bodily changes, 1935, Columbia University Press, New York, pages 279 to 290
- 13 (a) HENRY, G W Some roentgenologic observations of gastrointestinal conditions associated with mental disorders, Am Jr Psychiat, 1924, III, 681-685 Gastrointestinal motor functions in schizophrenia Am Jr Psychiat, 1927, VI, 135-152 Schizophrenia, Assoc for Research in Nerv and Ment Dis, 1925, V, 280-291 Gastrointestinal motor functions in manic-depressive psychoses, Am Jr Psychiat, 1931, LXXXVIII, 19
(b) DUNBAR, H F Loc cit Pages 290-316
- 14 WEISENBERG, T H, YASKIN, J C, and PLEASANTS, H Neuropsychiatric counterfeits of organic visceral disease, Jr Am Med Assoc, 1931, LCVII, 1751-1756
- 15 JAMES, W Principles of psychology, 1927, Holt, New York, II, 449
- 16 ALVAREZ, W C Ways in which emotions can affect digestive tract, Jr Am Med Assoc, 1929, XCII, 1231
- 17 MOSCHOWITZ, E Psychogenic origin of organic diseases, Arch Neurol and Psychiat, 1934, LXXXII, 903
- 18 WEISS, E Management of patient with essential hypertension, Pennsylvania Med Jr, 1936, XXXIX, 313
- 19 JONES, E Anxiety character, Med Rev of Rev, 1930, XXXVI, 177
- 20 YASKIN, J C Psychobiology of anxiety, Psychoanal Rev, 1936, XXIII, (supp), 1, 1937, XXXV, (supp) 25
- 21 HORNEY, K The neurotic personality of our time, 1937, Norton, New York, page 100
- 22 ADLER, A Study of organ inferiority and its psychical compensation, Nervous and Mental Disease Monograph Series, New York, 1917, No 24
- 23 YASKIN, J C The psychoneuroses and neuroses A review of 100 cases with special reference to treatment and end results, Am Jr Psychiat, 1936, XCIII, 107
- 24 VONDERAHE, A R Histopathologic changes in the nervous system in cases of peptic ulcer, Arch Neurol and Psychiat, 1939, XLI, 871
- 25 DUNBAR, H F, WOLFE, T P, and RICH, J McK Psychiatric aspects of medical problems, Am Jr Psychiat, 1936, XCIII, 649

FEVER THERAPY¹

By GORDON B. TAYLOR, M.D., F.A.C.P., Commander, (MC), U.S. Navy,
Philadelphia, Pennsylvania

WITHIN recent years more than 600 articles have been written on artificial hyperpyrexia and more than 50 diseases have been allegedly treated by this method of therapy. It is not my intention to condemn any fever-producing method used, to criticize any member of the profession for using any particular type of fever therapy which he may prefer and can best use, or to offer artificial fever therapy as a panacea for the correct and proper treatment for all diseases. I do intend briefly to review the current literature on the subject, to describe the method of treatment I have been taught to use in the Navy, namely, artificial fever therapy produced by the Kettering hyperthermia cabinet, and to report the results I personally have obtained in a series of cases of neurosyphilis and gonococcus infections during this year.

At the present time the most widely recognized therapeutic fever-producing agents are

1 *Foreign Proteins, viz., Typhoid and Paratyphoid Vaccines, Given Intravenously* However, these will not produce and maintain the necessary elevation of temperature desired, and consequently their use in the treatment of neurosyphilis, gonorrhea, and other diseases in which a high elevation of temperature is desired is of little practical value and has largely been replaced by the safer and more accurately controlled artificial fever by physical means.

2 *Malaria* Malaria was tried in Russia in 1937 for the treatment of gonorrhea, the patients' symptoms did not improve but were exaggerated. This treatment will not maintain a rectal temperature of 106° F. over a period of several hours and would, therefore, be of little value in the treatment of gonorrhea. On the other hand, malaria has been recognized for many years to be of definite proved value in the treatment of certain stages of syphilis, particularly dementia paralytica. Such authorities as John A. Kolmer, George Wilson and Paul O'Leary still prefer malaria to the artificial physical methods of producing hyperpyrexia.

Two factors which may interfere with the immediate use of malaria are its unavailability in certain localities and the patient's physical condition. Another factor to consider at this time is the increasing shortage of quinine, as this drug may be required to control the therapy of induced malaria.

From the clinical data available it appears that there is very little difference in the results obtained from the use of malaria and the use of the hyperthermia cabinet in the treatment of dementia paralytica. However, it is interesting to note that Ewalt and Ebaugh¹ in reporting 232 cases of de-

* Presented before the Fifth Annual Round-up of Eastern Pennsylvanians of the American College of Physicians, U.S. Naval Hospital, Philadelphia, Pa., October 23, 1942.
(Note: Authorization has been obtained from the Surgeon General for publication.)

mentia paralytica treated by both methods of therapy state that the artificial fever series was safer and produced the better results, also when contraindications to malaria were present, many cases could be safely treated with artificial fever therapy. Huntley² of Michigan in a series of 168 men with dementia paralytica who completed treatment, reports that he obtained 100 per cent clinical improvement and 83 per cent of serological remissions with artificial fever therapy. This work was done in a state prison where he had complete supervision of his patients with follow-up chemotherapy. With 29,726 hours of fever treatment he does not report a single fatal accident attributable to fever therapy. Neymann³ reports that two-thirds of a total of 114 cases of tabes dorsalis exhibited definite improvement after fever therapy. Krusen⁴ asserts that one of the most constant findings when physical fever is used in treatment for tabes dorsalis is the relief of gastric crises and tabetic pains. He also states that the best results are obtained in early cases both with tabes dorsalis and dementia paralytica. Interstitial keratitis, non-specific iritis and uveitis are said to respond readily to fever therapy.

My personal experience with the treatment of neurosyphilis has been limited. Available studies show that about 70 per cent of cases of dementia paralytica when properly treated with either malaria or physical means show marked improvement. It seems advisable to use the method of treatment and equipment which are most convenient and with which one is most familiar. Both malaria and artificial fever therapy are dangerous and should only be used in an institution with properly trained personnel and standard equipment.

3 Artificial Fever Therapy by Means of the Kettering Hypertherm Cabinet A few months ago Turville and Fetter⁵ reported 1101 fever treatments given to 173 patients in the Naval Hospital in Philadelphia during the two-year period July 1, 1940, to July 1, 1942. Of 38 patients treated for gonococcal infections they reported 87 per cent cured. Marked improvement occurred in 71 per cent of 32 patients treated for neurosyphilis. On the basis of their studies they believe that fever therapy is the treatment of choice in sulfanilamide-resistant gonococcal infections and in dementia paralytica, and is a valuable adjunctive treatment in other diseases. They further believe that the blood chlorides and nonprotein nitrogen are not disturbed to a point of danger if the patient takes and retains the prescribed amount of water and sodium chloride before and during the fever session.

Kendell, Rose and Simpson⁶ have reported marvelous results in a series of 31 unselected consecutive chemotherapy-resistant gonococcal infections treated by the combined method of artificial fever and chemotherapy. They reported 100 per cent cures in this series and stated they used rigid bacteriologic criteria for the basis of determination of this cure. They further reported that the time-dosage relationship greatly influenced the effectiveness of this method of therapy. When the drug is administered for 18 hours preceding fever treatment, the effectiveness is much greater than when it is

administered immediately prior to or during treatment. The blood concentration of the drug in the patient should be 1:10,000 or roughly 10 mg of the drug per 100 c c of blood at the time of the fever treatment. As shown by Wengatz, Boak and Carpenter,⁷ the thermal death time of certain strains of gonococci is lowered by approximately 50 per cent in the presence of a concentration of 1:10,000 sulfanilamide. On this assumption Simpson and his co-workers tried this therapy and reported their findings. These 31 cases were given a single 10-hour session after they had been on sulfanilamide for 18 hours and the blood concentration levels were approximately 1:10,000.

I have two series of my own cases to report. The first series consists of 23 cases of gonococcal infection treated at the National Naval Medical Center in Bethesda, Md., in the early part of this year. Nineteen of these cases were uncomplicated gonorrhea which were chemotherapy-resistant. All of these cases except two were cured with one long nine-hour fever session with rectal temperature between 106° and 106.8° F for seven hours. The other two cases required another short session of five hours each given on the third day, after which they were both clinically and bacteriologically cured. Two cases of this series had severe unilateral gonorrheal ophthalmia which responded readily to fever therapy. I have seen four severe cases of gonorrheal ophthalmia which were treated with artificial fever therapy and which responded as well as any disease responds to any type of therapy. One case had a severe panophthalmitis and a good ophthalmologist had recommended evisceration. The patient was given 10 hours of fever therapy at a rectal temperature of 106° F after proper preparation, and he returned to duty with 20/20 vision in the affected eye. The other two cases in this series had severe gonorrheal arthritis, received 10 five-hour sessions and improved to the extent that they both returned to a regular duty status. All of these cases received combined chemotherapy and artificial fever therapy, the technic of which will be described later. My second series of cases was treated at this hospital since July 1 of this year. It consists of 28 cases of chemotherapy-resistant gonococcal infections and four cases of neurosyphilis. All four of the neurosyphilis cases have shown marked clinical improvement. Further serological studies will have to be made. Twenty-four of the 28 cases of gonococcal infection were cured. In two cases the treatments had to be discontinued. The other two cases have shown very little or no response to this type of therapy.

In addition to the excellent therapeutic effects shown in gonococcal infection and syphilis, Prickman⁸ states "One cannot but be impressed in treating febrile cases of brucellosis by artificial fever, by the promptness of the resulting remissions, the absence of relapses, the almost immediate feeling of well-being, the gain in weight and strength and the patient's ability to return promptly to work. This has occurred in four out of five patients so treated."

TECHNIC OF FEVER THERAPY TREATMENT USED

This technic of treatment is not original. It is practically the same technic described by Krusen⁹ and by Simpson⁶ and their co-workers.

The patient is given a complete general physical examination the afternoon before treatment. He should have 24 hours' rest prior to treatment with a high carbohydrate diet and a moderate amount of forced fluids. Urine should be checked for amount and specific gravity for 24 hours prior to treatment.

Eighteen hours prior to time of starting treatment (if the patient is being treated for gonorrhea), he should be given as an initial dose, 4 grams

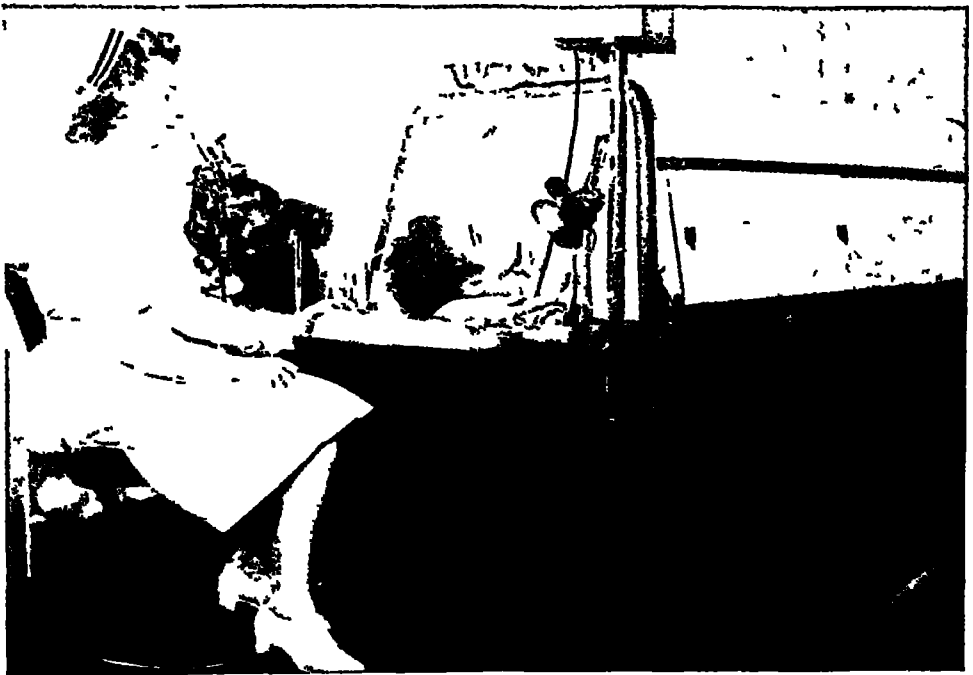


FIG 1 Patient with nurse and equipment during the high temperature period of fever therapy treatment.

(60 grains)—or 5 grams if he weighs more than 150 pounds—of sulfathiazole by mouth, followed every four hours day and night with 1 gram. This should bring the patient's blood level to a concentration of 1:10,000 by the time he acquires a high temperature. The patient is not given breakfast, but may have black coffee. A soap suds enema is given for convenience before he is put in the cabinet. It is well to give 1000 c.c. of 5 per cent glucose in normal saline prior to the patient's entrance into the cabinet. The patient should be shown how to use a B.L.B. mask and told he is going to be given oxygen prior to entering the cabinet, so he will know what to expect during the excitable stage. Fluids are not permitted copiously the first hour of treatment because this would precipitate vomiting. After the first hour

the patient is encouraged to drink 5 per cent salt solution, fruit juices and water. These fluids should be chilled but not iced. Pantopon gr 1/6 to 1/3 and codeine by mouth are the best drugs to use to control pain and restlessness while in the cabinet. I do not use morphine, if it is used it should be in small doses and repeated, never in large doses, during high elevation of

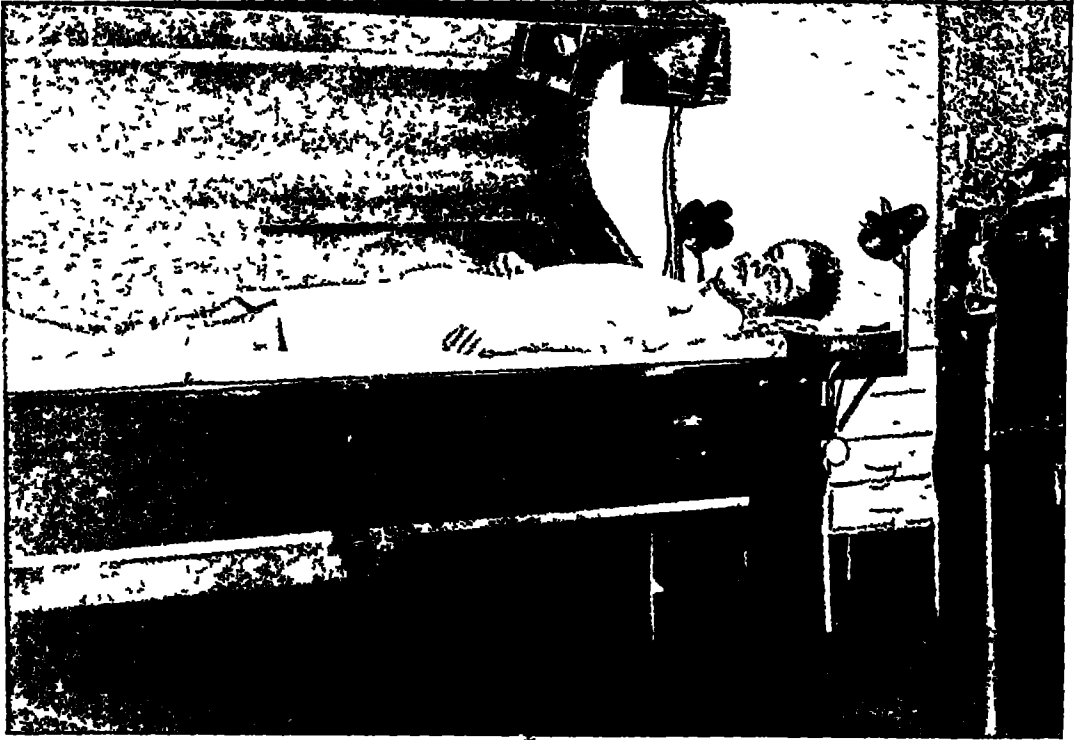


FIG 2 Patient after receiving 10 hours fever therapy by the Kettering hyperthermia method.

temperature. The patient should be watched very cautiously. He should be removed from the cabinet for any of the following reasons:

- 1 If he becomes unconscious at any time
- 2 If the blood pressure drops suddenly and there are symptoms of approaching cardiovascular collapse
- 3 If the pulse rate is above 160
- 4 If any untoward signs or symptoms you cannot explain develop. Remember the rhyme—"If in doubt, take him out."

Complications (1) Tetany. This is frequent but without bad results. It responds quickly to calcium gluconate. (2) Circulatory collapse. This picture is the same as severe surgical shock. I have seen two cases. The treatment is 100 c c of 50 per cent glucose, and supportive treatment. (3) Cramps of various muscles of the body. This can be prevented if patient takes and retains sodium chloride in proper amount. (4) Pulmonary edema. Rare. Treatment is venesection. Remove 500 c c of blood. (5) Cerebral edema. Rare. Treatment is spinal puncture.

Contraindications These are the same as for any major surgery

CONCLUSIONS

1 Fever therapy in combination with chemotherapy offers the best therapeutic weapon we have in treating gonococcic infections and neurosyphilis, particularly dementia paralytica. It is a valuable adjunctive therapeutic agent in the treatment of chorea, infectious arthritis and brucellosis.

2 After one unsuccessful trial of chemotherapy in all gonococcic infections, I strongly recommend and urge that the combined method of chemotherapy and artificial fever therapy be instituted.

BIBLIOGRAPHY

- 1 EWALT, JACK R, and EBAUGH, FRANKLIN S Treatment of dementia paralytica. A five year comparative study of artificial fever therapy and therapeutic malaria in 232 cases, Jr Am Med Assoc, 1941, cxi, 2474-2477
- 2 HUNTLEY, W B Syphilis treated with fever therapy in penal institutions, Arch Phys Therap, 1941, xii, 667-673
- 3 NEYMANN, C A Artificial fever produced by physical means, its development and application, 1938, Charles C Thomas, Springfield, Ill, p 28, fig 6
- 4 KRUSEN, FRANK H Physical medicine, 1941, W B Saunders, Philadelphia, Pa, p 122
- 5 TURVILLE, WM H H, and FETTLER, FERDINAND Experiences with fever therapy at the Philadelphia Naval Hospital, U S Naval Med Bull, 1943, li, 431-441
- 6 KENDALL, H WARLEY, ROSE, DONALD L, and SIMPSON, WALTER M Artificial fever versus combined fever-chemotherapy in gonococcic infections, Arch Phys Therap, 1941, xii, 103-110
- 7 WENGATZ, H F, BOAK, RUTH A, and CARPENTER, C M The bactericidal effect of sulfanilamide on the gonococcus in vitro, Jr Bact, 1938, xxv, 36
- 8 PRICKMAN, L E, BENNETT, R L, and KRUSEN, F H Treatment of brucellosis by physically induced hyperpyrexia, Proc Staff Meet Mayo Clin, 1938, xiii, 321-328
- 9 KRUSEN, F H Personal Communication

THE RELATION OF THE CARRIER TO EPIDEMIC MENINGITIS *

By J HOWARD MUELLER, PH D , *Boston, Massachusetts*

By way of orientation, it may be well to review briefly the facts, so far as they appear to be known, regarding the elements involved in the spread of epidemic meningococcal infection. We shall then be in a position to examine the evidence which supports certain of these matters and to call attention to the lacunae which still exist and which make it difficult to outline any reasonable program for control of this disease.

It has long been recognized that the meningococcus finds its normal habitat, as far as is known, in the human nasopharynx. Occasionally, and presumably from this focus, it enters the body and produces a septicemia and a meningitis. Also, and certainly more frequently, it leaves the throat on droplets of saliva expelled in talking, coughing or sneezing and finds a new abode in the nasopharynx of another individual. Careful examination of any large group invariably leads to the detection of carriers. Therefore, conditions favorable to the transmission of other respiratory disease should result in a rise in carrier rate.

During the last war much emphasis was placed on carrier studies. Overcrowding in barracks was shown to result in a gradual rise in the percentage of such individuals, and it was stated by Glover that when a certain critical level was reached, cases of meningitis began to appear. Doubt was later thrown on this by studies carried out by Dudley and Brennan in an English naval training station. During 1932 a number of sporadic cases of meningitis were accompanied by a carrier rate among contacts of only 13 per cent, whereas the following year, with no disease, a rate of 50 per cent was maintained.

Like many other bacterial species, the meningococci are serologically heterogeneous. Their classification is difficult, and even now relatively unsatisfactory. It is generally accepted, however, that Type I organisms are responsible for most epidemic disease, whereas other types are more likely to be encountered in the occasional sporadic case. Carriers of Type I organisms normally make up only a small proportion of the total. Therefore, in order to provide valid evidence, not only must the type of organism causing clinical disease be known, but the carrier strains must also be typed, for only the proportion of homologous organisms can be significant. Failure to provide this information goes far to invalidate a good deal of the older data.

* Presented before the New England Regional Meeting of the American College of Physicians, Boston, February 5, 1943.

From the Department of Bacteriology and Immunology, Harvard Medical School and School of Public Health, Boston, Mass.

There is a conviction, not yet entirely supported by experiment, that carriers of Type I organisms tend to be transient, whereas the other types, ordinarily of little or no pathogenic importance, may persist for long periods in their hosts. It is highly probable that many of the carriers who were placed in quarantine, often for months, during the last war, harbored Type II and were quite harmless.

Of Type I meningococci there are probably strains of varying degrees of virulence, and in man there are surely different levels of resistance to infection. Thus, an individual who acquires an organism of this type in his nasopharynx may suffer no ill effect, or he may develop the usual clinical infection of the meninges, or he may succumb within a few hours to a fulminating septicemia. Methods for the evaluation of virulence of meningococci as well as for testing host resistance are urgently needed in order to provide a sound basis for control measures. None of the attempts to reach an understanding of these factors has proved satisfactory, and it is to be hoped that the renewed interest shown at present in the matter will yield information which is badly wanted. Thomas, Smith and Dingle, at the Boston City Hospital and in our own Department have already uncovered certain possibilities which should be capable of application to these vexing problems.

It seems probable that a large proportion of our population is relatively immune to the meningococcus, possibly through harboring organisms of low virulence from time to time. It is also possible that the normal tissues of the nasopharynx provide a barrier which even a meningococcus of high virulence is unable to pass, but which may occasionally break down owing to mechanical injury or to other respiratory infection. In any case, enough information is at hand to offer a satisfactory explanation of certain of the phenomena of an epidemic. For example, it is usually difficult to trace direct contact between clinical cases, and we may assume that this is due to the fact that only an occasional individual who harbors the organism becomes actually diseased. The same virulent strain may, therefore, be passed from one healthy carrier to another through many hosts before it reaches one in which conditions for invasion are suitable. When this does occur, all trace of the intervening chain of passages has been lost.

Clearly, there are many problems for the bacteriologist and immunologist to solve before he is in a position to lay down plans for the control of epidemics. Our own work, thus far, has concerned itself with the rather elementary but essential matter of simplifying the methods used for the isolation and recognition of the meningococcus, and with the collection of data on carrier rates.

Traditionally, cultivation of this organism must be carried out on an "enriched" medium containing sterile ascitic fluid, serum or blood. The preparation of such a medium under field conditions in military units becomes extremely difficult, a fact which every bacteriologist involved in the matter during the last war well remembers. The British at that time used a

medium in which the ascitic fluid was replaced by an extract of dried peas, presumably because of the high protein content of this seed. When properly made, it was entirely satisfactory, but its preparation was troublesome. We have now found that this medium can be greatly simplified. Its efficacy was due, not to the protein of the pea meal, but to the starch. Ordinary laundry or corn starch is effective, and the complete medium can be readily prepared from ingredients easily obtainable. It can be autoclaved and stored and is well suited to field use.

Another most troublesome matter was the fact that the meningococcus very quickly dies on a swab when chilled. It was customary, therefore, to carry the culture medium in Petri plates to the site at which cultures were to be taken. They were transported in water jacketed cases kept at body temperature, inoculated directly, and kept warm until they could be returned to an incubator. This difficulty, and the accompanying limitation of the number of cultures which could be taken, has now been overcome. Cox, McDermott and the writer have shown recently that *gonococcal* material for culture can be preserved even for two or three days, over a considerable temperature range, by immersing the swab in a few drops of sterile horse blood, thus making possible shipment of specimens through the mail. We have found this equally applicable to the meningococcus, and by this means have materially simplified the matter of carrier examinations in the field.

Typing of the strains which are isolated is carried out by a rapid and simple method which I believe was devised by Julia Parker and Zinsser many years ago, and appears not to have been published. It makes possible the ready identification of Type I, many strains of Group II and the new Type II alpha. We have made no effort to classify the remaining strains, which are probably of no epidemiologic importance, but place them in "Group X."

These methods have been used in our laboratory for more than a year in following the carrier incidence of two fairly large communities. About 100 cultures are taken twice weekly from each of these, and worked through. The following table shows the result of this study.

TABLE I

	% Total	% I
Jan 1942	18.6	3.1
Feb 1942	21.7	2.5
Mar 1942	25.7	3.6
April 1942	29.0	4.9
May 1942	25.0	3.6
June 1942	22.8	3.6
July 1942	30.1	5.1
Aug 1942	20.6	3.3
Sept 1942	24.4	3.6
Oct 1942	28.7	2.6
Nov 1942	29.4	3.8
Dec 1942	32.7	7.4
Jan 1943	25.6	10.1

In order to condense the data, only the total carrier rate for all strains of meningococci and the Type I figures are given. Those relatively few

cases of the disease which have occurred in these communities during the period of time covered and from which we have been able to get cultures, have all been due to Type I. It is noteworthy that the total carrier rate has been remarkably constant, showing no evidence of seasonal variation. Equally striking is the low and constant incidence of Type I carriers up until two months ago. The rise since that time is definite and may well prove to be significant.

We have recently had an opportunity to cooperate in a study of the carrier situation in another community of individuals living in relatively close contact, during the course of a rather sharp outbreak of Type I infections. Between 60 and 70 per cent of a group of several hundred who were cultured were found to be carriers of the same type.

The problem of what to recommend, in a situation of this sort, is difficult in the extreme. One must naturally adopt the usual measures for minimizing respiratory transfer. Actual quarantine is probably out of the question. An experiment carried out on a group of approximately 400 of these individuals provided remarkably interesting evidence of one possibility which, however, is not without its drawbacks. Half the members of this group were fed sulfadiazine on three successive days, three grams the first and two grams each on the following days. The other half of the group served as a control. Three days after cessation of the drug all were cultured. The Type I carriers in the control group had increased from 68 per cent to more than 70 per cent. Of the 200 who had received sulfadiazine, not a single one carried a meningococcus of any sort. After a further lapse of three weeks, cultures were obtained on 116 of those treated with sulfadiazine. Of these, 18, or about 16 per cent, were found to be carrying Type I meningococci. Remarkably enough, nine of these 18 occurred in the throats of men who had been negative on the initial culturing. In other words, half of the men who have acquired a Type I meningococcus in the three weeks' interval are from the group of 32 per cent *originally negative*. This would appear to afford some support for the view that transient contact with this organism leads to a measure of resistance against it.

It appears, therefore, that in an emergency it may be possible to eradicate carriers from a given group of individuals, at least temporarily. One would have to balance the necessity against the possible dangers of such a procedure before undertaking it. Except for such a method, no means is known for artificially clearing up the condition.

Fortunately, the mortality of meningitis has been greatly reduced by the use of the new drugs. In spite of this, it remains a distinctly serious disease, and one must hope for advances in our knowledge of its immunology which can lead to more effective measures for its elimination.

CARCINOMA OF THE LUNG; A REVIEW OF 31 PROVED CASES AT THE PHILADEL- PHIA NAVAL HOSPITAL *

By FERDINAND FETTER, M D , F A C P , Lieutenant Commander, Medical
Corps, United States Naval Reserve, *Philadelphia, Pennsylvania*

INCIDENCE AND ETIOLOGY

THE outstanding fact about primary carcinoma of the lung is the amazing increase in its frequency during the past 30 years. Formerly bronchogenic carcinoma was considered one of the rare forms of cancer, now it has been found to be one of the commonest. Some startling facts about the frequency of this disease that were brought out by Overholt and Rumel¹ in a recent review of the subject are (1) that large autopsy series show that approximately 10 per cent of all cancers start in the lung, (2) that about 15,000 people die from bronchogenic carcinoma each year in the United States, and (3) that the lung is now the second most common site of origin of primary malignancy, being exceeded only by the stomach. In fact, Halpert,² on the basis of a 10 year survey of necropsies at the Charity Hospital in New Orleans, predicts that carcinoma of the lung will soon be the commonest malignancy in the male, more frequent even than carcinoma of the stomach.

With such an astounding increase during the past three decades in the number of cases of this disease that are being diagnosed, both ante- and post-mortem, it is natural that causes for this are being looked for. A few pathologists still believe that the increased incidence is apparent rather than real. By this they mean that more cases are being found now because they are being looked for by pathologists and clinicians who are "bronchogenic carcinoma conscious," but that actually there has not been an increase in the number of cases during the past four to five decades. However, the majority opinion among both clinicians and pathologists is that the present high incidence of primary lung cancer represents an actual increase in its frequency.

As to the real cause of the disease, or even reasons for the sudden jump in its incidence, we are still pretty much in the dark. The only etiologic agent that seems to be a definite factor does not apply to the great number of people who develop the disease. This factor is the inhalation of radioactive substances. At the Schneeberg mines, where pitchblend is obtained as a source of radium, 62 per cent of the workers are reported³ to develop carcinoma of the lung. Factors proposed⁴ which are more widely applicable as a cause of the disease, and incidentally of its increased incidence are the influenza epidemic of 1918 (metaplasia of the bronchial mucosa has been found in patients dying of influenza), inhalation of irritating fumes such as

* Read at the Fifth Annual Round-up of Eastern Pennsylvanians of the American College of Physicians, U S Naval Hospital, Philadelphia, Pa, October 23, 1942

exhaust from automobiles or fumes from tarred roads or tobacco smoke (the fact that carcinoma of the lung is at least four times as common in men as in women has been cited in support of the tobacco smoke theory), silicosis, tuberculosis, and other non-specific lung infections as bronchiectasis or lung abscess. However, no one has been able to establish any of these agents as being really important as a cause of the disease, or as a cause of its increased incidence. As is the case with most cancers elsewhere in the body, we are still basically ignorant of the cause of primary carcinoma of the lung.

CASES SEEN AT THE PHILADELPHIA NAVAL HOSPITAL

In the 21 month period between January 1, 1941, and October 1, 1942, there have been 31 proved cases of primary carcinoma of the lung admitted to the Naval Hospital in Philadelphia, and 16 more cases in which this diagnosis was established to the satisfaction of all concerned, but in which microscopic proof was lacking. All of these cases occurred in veterans, and none in active service patients. A previous report⁴ of cases of this disease from this hospital, covering the 31 month period from January 1, 1937, to August 1, 1939, consisted of 30 proved cases. It is obvious, therefore, that the incidence of the disease in the veterans admitted to the Philadelphia Naval Hospital is increasing. This increase is even greater than it seems, since the number of veterans admitted per year to the hospital during the period included in this report was actually less than during the period of the first report.

Symptoms and Signs There are, unfortunately, no symptoms or physical signs that are pathognomonic of carcinoma of the lung. In this series cough and sputum were the most common symptoms, being present in all but one of the patients. Two other common symptoms, which often were actually responsible for the patient's admission to the hospital, were chest pain, which occurred in 75 per cent of the cases, and hemoptysis, which occurred in 60 per cent. Other symptoms frequently complained of were loss of weight, weakness, shortness of breath, and wheezing or asthma. All of these symptoms obviously could belong to many other chronic lung diseases, as tuberculosis, lung abscess, or bronchiectasis.

Abnormalities on physical examination of the chest were present in all cases, but they too were not pathognomonic, and simulated the findings in other chronic lung diseases. Since bronchogenic carcinoma often produces bronchial stenosis eventually and since most of our patients were first seen relatively late in the disease, signs of atelectasis in the portion of the lung distal to the bronchial occlusion were the most common physical signs suggesting the disease, and were present in 55 per cent of the cases. In 25 per cent of the patients, pleural effusion was present when the patient was first seen.

Roentgen-Ray Changes All of the patients in this series showed abnormalities on chest roentgen-ray. Unquestionably, the chest roentgen-ray

is the first important procedure, after the history and physical examination have been done, in establishing the diagnosis of carcinoma of the lung. It is possible, however, to have a normal chest roentgen-ray in an early case. Four per cent of Overholt and Rumel's¹ series of 75 cases had negative chest roentgen-rays, because the tumor itself was not radiopaque, and because changes in the lung tissue surrounding the tumor had not yet taken place. In a later paper, Overholt⁵ has emphasized the importance of routine chest roentgen-rays of men over 40 years in case-finding in lung cancer, comparing its importance to routine chest roentgen-rays of young adults in case-finding in pulmonary tuberculosis.

In this series of cases, the most important roentgen-ray finding suggesting lung cancer was atelectasis distal to the tumor, with accompanying shift of the mediastinum toward the affected side. This occurred in 65 per cent of the patients. Figure 1, the chest roentgenogram of patient S C U taken May 28, 1941, showing partial atelectasis of the right lower lobe, is typical of this group. Bronchoscopic biopsy showed squamous cell carcinoma. Thoracotomy was done on July 28, 1941, but the case was found to be inoperable because of extensive diaphragmatic adhesions. The patient was



FIG 1 Chest roentgenogram of S C U taken May 28, 1941, showing partial atelectasis of right lower lobe. Bronchoscopic biopsy showed squamous cell carcinoma.

subsequently given roentgen-ray therapy, and is still alive and in fairly good condition

Another type of lesion seen by roentgen-ray, less common than the atelectatic type described above, is the single circumscribed lesion, which is usually peripheral and beyond the reach of the bronchoscope. Fifteen per cent of our cases belonged to this group. Figure 2, the chest roentgenogram of pa-

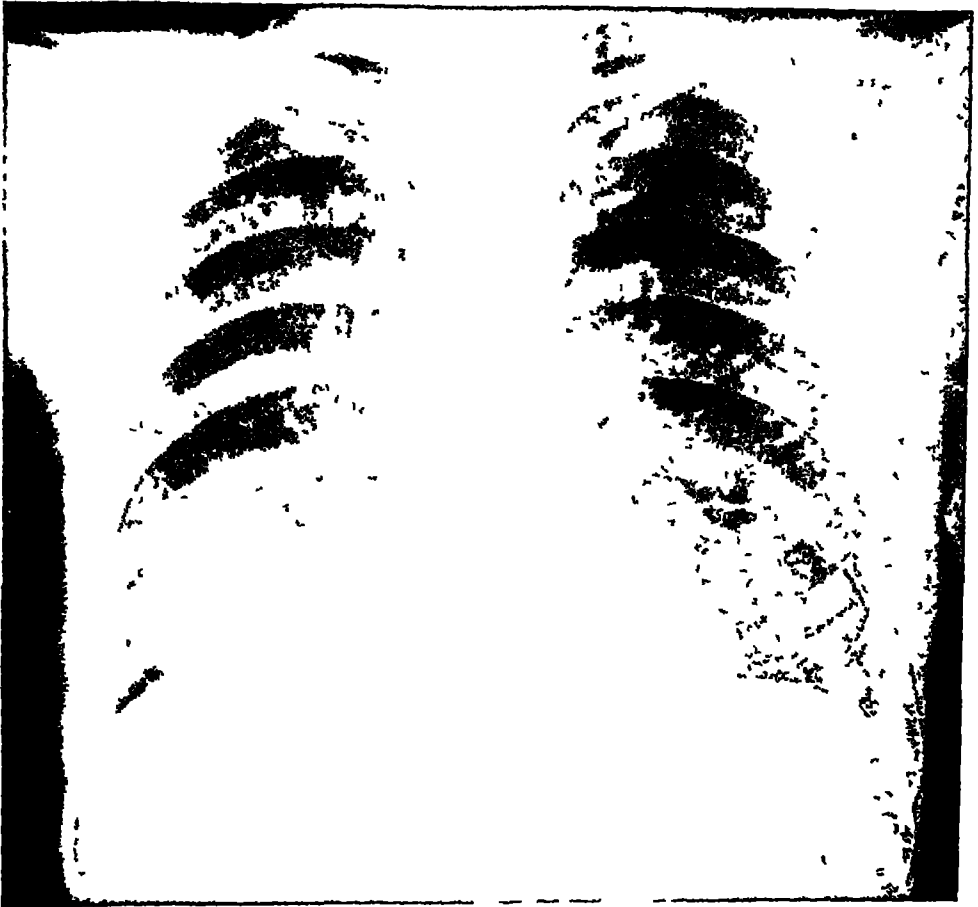


FIG 2 Chest roentgenogram of J. E. F. taken June 24, 1942, showing a circumscribed lesion in the right lower lobe, proved at autopsy to be adenocarcinoma

tient J. E. F. taken June 24, 1942, showing a circumscribed lesion in the right lower lobe, is fairly typical of this group. This patient, whose presenting symptoms were such that he was admitted to the neurological service, was too sick during his period of hospitalization to be bronchoscoped. Autopsy showed primary adenocarcinoma of the lung, with metastases to the brain and adrenal glands.

METHODS OF ESTABLISHING THE DIAGNOSIS

1 Bronchoscopic Examination and Biopsy This is the most important diagnostic procedure in establishing a positive diagnosis of bronchogenic

carcinoma About three-quarters of all primary carcinomata of the lung have been found to be within reach of the bronchoscope Bronchoscopic examination should not be postponed in any suspicious case In general, the course of the disease is rapid, averaging eight to nine months in untreated cases from onset of symptoms to death, so that a month's delay in establishing the diagnosis by bronchoscopy may make the difference between an operable and an inoperable case In addition to establishing the diagnosis, bronchoscopic examination often helps determine, by localizing the tumor, whether or not a case is operable, and may also improve a patient's health, by draining a suppurative process distal to the tumor

Bronchoscopic examinations, often repeated, were done in all but six of the proved cases in this series, and in all of the suspected cases Biopsies were taken if any abnormal tissue was seen through the bronchoscope The six cases not bronchoscoped were too ill during their period of hospitalization to tolerate this procedure Positive bronchoscopic biopsies were obtained in 14 of the patients bronchoscoped, 45 per cent of the proved cases

2 *Bronchography with Iodized Oil* This procedure helps to make the diagnosis in a few cases, but is not nearly as valuable as is bronchoscopy It was used in 12 of our cases It cannot establish a positive diagnosis by itself, of course However, when it shows bronchial stenosis proximal to an area of atelectasis in a suspected case, it gives pretty definite proof that a tumor is present, as it did in patient J C M Figure 3 shows this patient's chest roentgenogram taken June 2, 1942, after the installation of lipiodol A biopsy could not be obtained in three bronchoscopic examinations, because abnormal tissue was not seen through the bronchoscope This patient has recently died Autopsy showed primary adenocarcinoma of the lung, with metastases to the bones, brain, liver, and adrenal glands

3 *Examination of Pleural Fluid for Tumor Cells* In only one of the 12 cases in which pleural fluid was present was the diagnosis established by finding tumor cells in the fluid The finding of tumor cells in pleural fluid shows that the case is inoperable, since it means that extension of the tumor to the pleura has already taken place In fact, it is generally believed that the presence of pleural fluid in a case of lung cancer makes the case inoperable, whether tumor cells are found in it or not

4 *Examination of Sputum for Tumor Cells* This procedure has only limited application, it did not establish the diagnosis in any of our cases

5 *Aspiration Biopsy of the Lung* This procedure was not used in any of our cases It is almost universally condemned as being too dangerous because of the possibility of air embolism Furthermore, as Overholt⁶ has pointed out, surgical exploration is indicated in any case in which aspiration biopsy is done, regardless of the outcome For if the result is positive, the case should be operated upon anyway, and if it is negative, exploration will have to be done to establish the diagnosis

6 *Exploratory Thoracotomy* Lung surgeons now believe that in a suspicious case exploratory operation should be performed to establish the

diagnosis and determine operability, provided there is no evidence of metastasis and the patient is in reasonably good health otherwise. In this series, exploratory thoracotomy was the method of establishing the diagnosis in two cases. Unfortunately, both of these patients were found to be inoperable, because of extension of the growth beyond the limits of removability.

7 Biopsy from a Metastasis This was the method of establishing the diagnosis in three of our cases. In one patient, the metastasis was in an



FIG 3 Chest roentgenogram of J C M taken June 2, 1942, after lipiodol installation, showing stenosis and obstruction of the left lower lobe bronchus proximal to a lesion in the left lower lobe, proved at autopsy to be adenocarcinoma.

axillary lymph node, in one it was in a supraclavicular lymph node, and in the third it was in the subcutaneous tissues of the left upper arm. Cases in whom the diagnosis is established by this method are obviously inoperable.

8 Autopsy This is, of course, the final but certainly least desirable method of establishing the diagnosis in a suspected case. In 11 of our cases the diagnosis was finally established by this method. In all of them, however, the correct antemortem diagnosis of carcinoma of the lung had been made.

Table 1 summarizes the method by which the diagnosis was established in the 31 proved cases

TABLE I
Method of Establishing the Diagnosis

Method	Number of Cases	Percentage of Cases
Bronchoscopic biopsy	14	45
Necropsy	11	35
Biopsy from metastasis	3	10
Operation	2	7
Tumor cells in pleural fluid	1	3
Total	31	100

Microscopic Type Of the many classifications of the microscopic appearance of bronchogenic carcinoma, the simplest and most widely used is that which divides them into the differentiated, including squamous cell or epidermoid carcinoma and adenocarcinoma, and the undifferentiated (oat cell carcinoma). Combinations of any two or of all three forms may be present in the same specimen. The squamous cell type is the commonest and, as a rule, the slowest growing. In this series of 31 cases, 16 were squamous cell carcinomata, four were adenocarcinomata, and 11 were undifferentiated or mixed types.

Treatment As in all cancers, two forms of treatment are available, radiation and surgery.

Radiation Therapy There has been a good deal of argument as to the place of roentgen-ray therapy in cancer of the lung. Proponents of roentgen-ray therapy cite the case of a five-year survival after this form of treatment reported by Harper.⁶ However, Block's report⁷ of an eight-year survival without any treatment at all makes Harper's case less significant. Overholt and Rumel¹ found that patients who received high voltage roentgen therapy in cancericidal doses lived, on the average, only two-thirds as long as did untreated patients. There is general agreement that roentgen-ray has failed as a curative agent in lung cancer, and that it should be used only as palliative treatment in inoperable cases, to relieve such symptoms as pain or dyspnea. Of the proved cases in this series, roentgen-ray therapy was used in 16 inoperable cases, including four of the six cases in which exploratory thoracotomy had been done. In no case was the patient cured, but in about half there was marked relief of symptoms, and the patients were more comfortable than before treatment.

Surgical Treatment Of our 31 proved cases, seven were considered candidates for exploratory thoracotomy. One of these refused to be operated upon. Unfortunately, all of the other six patients proved inoperable because of extension or metastasis of the lesion, or because of too extensive pleural adhesions. One of these six patients died on the fourth postoperative day. The other five survived the operative period. One of these died 10 months later of cerebral metastases; the other four are still living, 16 months, seven months, one and one-half months, and one month respectively after the

operation In all of the patients who died and were autopsied, metastases were present, proving the cases inoperable In the other patients not operated upon, including both the suspected and proved cases, either evidence of metastases was present or other complicating factors such as old age, diabetes, or heart disease, which made the surgeons hesitate to perform such an extensive operation

Fate of the Patients in This Series Of the 31 proved cases, 16 have died and have been autopsied, six have died and were not autopsied, eight are living, most of them with evidence of metastasis, and one has been lost sight of Of the 16 unproved cases, four died and were not autopsied, eight are known to be living, most of them with evidence of metastases, and four have been lost sight of

DISCUSSION AND COMMENT

It is generally agreed that surgical removal offers the only hope of cure of carcinoma of the lung Thoracic surgeons now believe exploratory thoracotomy to be indicated, if an expert is available, in any suspected case of lung cancer, provided there is no evidence of metastasis and the patient is in reasonably good health otherwise They draw the analogy to exploratory laparotomy in suspected cases of carcinoma of the stomach or colon The recent report of Overholt⁷ shows that exploratory thoracotomy should not be reserved for proved cases Of 30 suspected cases of lung cancer that he explored, 13 removable malignant lesions were found

The mortality of the operation in the hands of experienced chest surgeons is rapidly decreasing For example, Overholt's¹ mortality was 33 1/3 per cent from 1933 to 1936 Since then, he has reduced this to 16 2/3 per cent The outlook for recovery obviously depends on the skill and experience of the surgeon who is operating In Overholt's⁸ series of 31 pneumonectomies for operable lung cancer, almost half of the patients, 13, were alive and well and free from evidence of recurrence or physical deformity several years after operation, three of these patients had survived more than five years Graham⁹ has one patient living and well nine years after operation, one patient who has remained free of symptoms for six years after operation, two five-year cures, and 20 patients alive and well more than one and one-half years after operation Graham⁹ has emphasized the hopeful aspects of surgery for lung cancer, citing the fact that this type of surgery is further advanced in its first 10 years of life than was surgery for cancer of the colon at the end of its first 10 years There is no doubt that, in the hands of the real experts in thoracic surgery, such as Graham, Overholt, Rienhoff, Churchill, and others, the outlook for patients with bronchogenic carcinoma is comparatively good, and as more and more men are trained in thoracic surgery, more and more patients will be cured In the hands of general surgeons, however, the operative mortality of pneumonectomy is high, and most of them, quite rightly, hesitate to attempt the operation

All in all, the outlook for most of the thousands of patients who develop carcinoma of the lung each year is still far from good. This is shown by the fate of the patients in this series and by the recent report of Perrone and Levinson,⁹ who found that operation could be considered in only three of their 77 patients with positive bronchoscopic biopsies. In the great majority of cases, carcinoma of the lung still remains a highly fatal disease for two reasons: (1) the difficulty and delay in establishing the diagnosis; and (2) the technical difficulties involved in surgical removal of the diseased lung even in operable cases. It is up to the general practitioners and internists to appreciate the great frequency of primary lung cancer and to see that, with the aid of roentgenologists and bronchoscopists, cases are diagnosed early and referred for surgery while they are still operable. It is then up to the surgeons to continue the truly remarkable reduction of the operative mortality in pneumonectomy they have already effected and to see that more surgeons, who can maintain this low operative mortality, are trained in this highly difficult and specialized field. I hope and believe that the outlook for these patients will become increasingly better and that carcinoma of the lung will eventually become one of the relatively curable types of cancer.

SUMMARY

During the 21 month period between January 1, 1941, and October 1, 1942, there have been 31 proved and 16 suspected cases of carcinoma of the lung among the veterans admitted to the Naval Hospital in Philadelphia.

Of the proved cases, the diagnosis was established by bronchoscopic biopsy in 14 cases, by necropsy in 11 cases, by biopsy from a metastasis in three cases, by exploratory thoracotomy in two cases, and by finding tumor cells in the pleural fluid in one case.

Seven cases were considered candidates for exploratory thoracotomy. One of these refused to be operated upon. All of the other six cases proved to be inoperable. One of these died four days postoperatively, one died of cerebral metastases 10 months after operation, and four are living. The other patients were considered inoperable because of evidence of extension or metastasis, or because of other complicating diseases.

In order to reduce the mortality of this disease, its great frequency must be constantly kept in mind, bronchoscopy must be performed early in suspected cases, and exploratory thoracotomies must be done by men specially trained in thoracic surgery in suspected as well as proved cases without evidence of metastasis.

BIBLIOGRAPHY

- 1 OVERHOLT, R. H., and RUMEL, W. R. Clinical studies of primary carcinoma of the lung, *Jr Am Med Assoc*, 1940, cxiv, 735.
- 2 HALPERT, B. Carcinoma of the lung, *Jr Am Med Assoc*, 1941, cxvii, 1090.
- 3 OSCHNER, A., and DEBAKEY, M. Carcinoma of the lung, *Arch Surg*, 1941, xlii, 209.

- 4 MAHER, P P, and STADERMAN, A H Bronchogenic carcinoma—Review of thirty verified cases, U S Naval Med Bull, 1941, xxxviii, 541
- 5 OLFRIHOLT, R H Carcinoma of the lung as a surgical problem, Am Jr Surg, 1941, liv, 101
- 6 HAKKER, F R Bronchogenic carcinoma of more than five years' duration treated by radiotherapy, Jr Thorac Surg, 1939, viii, 683
- 7 BROCK, R C Pulmonary new growths pathology, diagnosis, and treatment, Lancet, 1938, ii, 1103
- 8 GRAHAM, E A, in discussion of SHFNSTONE, S Experiences with total pneumonectomy, Jr Thorac Surg, 1942, xi, 413
- 9 PFERONE, J A, and LEVINSON, J P Primary carcinoma of the lung, ANN INT MED, 1942, xii, 12

PROBLEMS OF FLUID BALANCE IN THE TRAUMATIZED PATIENT *

By JONATHAN E. RHOADS, M D , Sc D (MED),
Philadelphia, Pennsylvania

FROM the standpoint of therapy, body fluids may be considered as composed of water, sodium chloride, glucose, basic ions such as sodium, acid ions such as chloride and the protein and cellular constituents of the blood. There are, of course, numerous other solutes in the plasma such as calcium, magnesium, and potassium chlorides, urea and various phosphates, but with the exception of calcium in certain unusual conditions the need for parenteral administration of these substances has not been demonstrated.

Perhaps the commonest disturbance of fluid balance due to trauma is blood loss as in hemorrhage. In this condition all of the body fluids are lost, but the reduction in blood volume is the serious factor in acute hemorrhage and the reduction in the hemoglobin is apt to be the most serious factor in chronic or repeated hemorrhage.

For this reason it has been shown by Best and Solandt that plasma is extremely satisfactory in the treatment of acute hemorrhage in a previously healthy individual. It should not, however, be used in one who was anemic previous to his hemorrhage nor is it adequate to use again and again in cases of repeated hemorrhage.

Patients with abdominal injuries may require suction drainage, they may develop intestinal obstruction; or they may develop intestinal fistulae. Consequently they may present as complicated problems in fluid balance as any that can be encountered. Furthermore, the traumatized patient may be dehydrated prior to his injury as the result of a lack of water, or a diarrhea due to infection of the intestinal tract. It is impossible, therefore, to segregate the problems of fluid in the traumatized patient from the problems of fluid balance in general.

Imbalance is not always due to a discrepancy between intake and output but may also be due to a shift of fluid within the body. The outstanding example of this is the shift of plasma from the intravascular to the interstitial spaces in patients with burns and in certain other types of traumatic shock. In these cases there is a special and urgent indication for plasma transfusions. This phase of the subject is being presented by Dr. Walter Estell Lee in his paper entitled "The Crush Syndrome and Burns."

The needs of patients with disturbed fluid balance have been recognized qualitatively for a good many years. The investigations of the last few years, however, have emphasized the need for quantitative methods in the correction of these disturbances.

* Presented October 22, 1942, at a program of Postgraduate Nights arranged by the American College of Physicians at the United States Naval Hospital, Philadelphia.

Although it is true that three liters of physiological saline solution a day may permit the average patient to regain water balance, salt balance, and acid base balance, direct observations on numerous individual patients will show dangerous variations in salt and water retention and in some cases a failure to attain a normal acid base equilibrium.

Fortunately water and salt balance seldom become problems in the acutely traumatized patient for 12 to 24 hours unless the trauma has been preceded by a disturbance such as from excessive perspiration or water deprivation. This interval may allow time for the evacuation of the more complicated cases to areas where the aid of a laboratory is available. During this early period plasma and occasionally whole blood in addition will usually be indicated.

In observations on burn cases at the Pennsylvania Hospital we have been impressed with the fact that the pulse volume and particularly the skin temperature of the extremities were valuable guides in the administration of plasma. In general if the plasma volumes estimated from the hemoconcentration did not fall below 70 per cent of normal, the peripheral circulation was well maintained. In instances in which the peripheral circulation was poor it would, as a rule, become satisfactory when enough plasma had been given by transfusion to restore the plasma volume to 70 per cent of normal. Even without the benefit of hematocrit or hemoglobin determinations it should be possible to gauge the administration of plasma fairly satisfactorily on the basis of the peripheral circulation.

Estimation of Water Deficits In patients who are under continuous observation it is customary to estimate the water deficit by dead reckoning. A certain amount is allowed for insensible loss, and loss by other avenues is measured or estimated.

If patients show signs of dehydration when first seen, however, it is important to realize that an extensive deficit must be assumed. Coller and his associates consider that this usually amounts to 6 per cent of body weight or approximately a gallon and a half for a large man. The deficit may of course be substantially greater than 6 per cent in severe dehydration.

Such an individual, should he have to undergo anesthesia and operation, might require eight to ten liters of fluid during his first 24 hours of hospitalization.

Estimation of Salt Deficits The chloride concentration is most often disturbed in one of two ways. Either there has been excessive loss of salt-containing perspiration which has been replaced by ordinary drinking water, or there has been an excessive loss of gastrointestinal juices compensated by the administration of fluids containing little or no salt. Coller and Maddock's rule of half a gram of salt per kilogram of body weight for a hypochloremia of 100 mg per 100 cc below normal has been very helpful. With severe losses the sodium chloride has sometimes been given intravenously in 2 per cent solution, but in most instances it may be given satisfactorily at the isotonic concentration of 0.85 per cent.

In patients with hypoproteinemia or in dehydrated patients with normal plasma protein concentrations it is unwise to give the full amount of salt at once as such patients may develop peripheral and pulmonary edema

Quantitative Correction of Disturbances in Acid Base Balance Disturbances due to the formation of ketone bodies either as the result of diabetes or of starvation generally respond well to the administration of glucose and saline solutions (with insulin if indicated) At certain times, however, it is valuable to have a parenteral method of correcting a reduction in the CO_2 combining power of the plasma rapidly

In these cases one-sixth molar sodium lactate solution may be employed One and eight-tenths c c per kg of body weight may be allowed for each one volume per cent change desired in the CO_2 (Hartmann)

Until recently no clinically tested method has been available for overcoming alkalosis by parenteral means During the last few months ammonium chloride solutions have been employed for this purpose by Zintel, Rhoads and Ravdin at the Hospital of the University of Pennsylvania On the average 1.2 gm of ammonium chloride have resulted in a reduction of one volume per cent in the plasma CO_2 in a 150 pound person This is approximately equal to 2 c c of sixth molar solution per kg of body weight

The trial of this method has been limited and cannot be stated to be of proved safety No serious reactions have been encountered in the group of patients who received it, however, and it should be considered when alkalosis nephrosis is threatened and when the oral route is not available

SUMMARY

The importance of correcting disturbances in fluid balance as quantitatively as possible is stressed

Methods of estimating the electrolyte requirements of patients with hypochloremia and with disturbed acid base equilibrium are discussed

THE RELATION OF THE CRUSH SYNDROME TO THAT OF BURNS AND OTHER TYPES OF TRAUMATIC WOUNDS OF HUMAN TISSUES *

By WAITER ESTELL LEE, M D , *Philadelphia, Pennsylvania*

THE purpose of this paper is to call attention to evidence which is gradually accumulating that such diverse traumatic injuries as (1) *blast*, (2) *burns*, (3) *crush*, and (4) *trauma of the soft tissues* all probably have at least two etiological factors in common (1) The loss or escape of plasma from the circulating blood stream, and (2) a toxemia resulting from degenerative changes and products liberated from dying or dead tissue cells, plasma and bacteria

The subject chosen, the relation of the *crush syndrome* to that of *burns* and other *types of traumatic wounds* of human tissues, represents an obsession of ours which is the result of an experience in France during World War I, and which at last has been confirmed experimentally by Blalock and reported in the October 1942 number of *Surgery, Gynecology and Obstetrics*. In this paper he discusses the syndrome of several types of injuries dealing with a conglomeration of reactions to *tissue damage* which, at present, are grouped together under the term *shock*. He suggests it might be wise if the term shock could be abolished altogether, but we agree that common usage makes this impossible at the present time.

No one will question the advances which have been evolved in surgical treatment since the last war and the relatively astounding results now being obtained in the treatment of trauma. In burns alone, before 1914, a hospital mortality of 80 per cent in severe massive, third degree burns was accepted, whereas at the present time reports from the Council of Medical Research show an average mortality in this type of burn of from 7 to 10 per cent.

My theme during these years has been that this gradual lowering of the mortality, decrease in length of hospitalization and lessening of the disfigurement and permanent disability from scar tissue in burns is due to appreciation of the fact that *burns are open traumatic wounds*, and to hear Blalock classify them with hemorrhage, trauma to large masses of muscle, blast, crush injuries and postoperative complications, etc., would seem to justify our teaching.

Blast Little was known about the nature of this injury until the present war and practically all the clinical knowledge we now have about it is based upon reports from the British. Zuckerman and his associates, in 1942, reported in the *Lancet* their experiments with rabbits which were directly ex-

* Read before the meeting of the Postgraduate Nights of the American College of Physicians held at the Naval Hospital, Philadelphia, October 22, 1942

posed to high blast pressures (from which their respiratory systems were protected) in which they found abdominal and thoracic lesions caused, they believe, by a wave acting upon the *surface* of the body and not, as previously supposed, by either the pressure or suction components of the wave acting through the nose and mouth. They conclude that both the thoracic and abdominal lesions may be due primarily to the impact of the pressure component on the body wall and that these lesions can occur when the suction component is excluded.

Immediate death, unassociated with evidence of external trauma in some instances, may be due to occlusion of the large bronchi by blood clot. *Delayed death* is usually due to pulmonary edema and less often to intraperitoneal hemorrhage. In the reports from their clinical experiences with civilians, however, intrapulmonary hemorrhage of some kind is the most frequent finding, making this one condition in which blood transfusion or blood substitutes are contraindicated whereas morphine and oxygen are required. It would seem then that from the clinical and experimental evidence, injuries to pulmonary tissues by blast may result from direct trauma through the respiratory system or indirectly by pressure upon the body surface.

Burns Our main reference to the problem of burns will be to point out the similarity of the basic tissue damage and tissue reaction to what are now called crush injuries and probably also to blast injuries.

As early as 1931, Underhill and Blalock found that there is an unusual escape of the blood plasma into the perivascular tissues in this type of injury, and Blalock stated that the loss of such relatively large amounts of plasma from the circulation must be an important cause of the decrease of circulating blood volume which is at least the initiating factor in the decline of blood pressure. Following the reduction of blood volume and the increase in blood concentration many vicious derangements in the physiology of the tissues take place: (a) Decreased elimination by the kidneys; (b) Imbalance between intra- and extracellular fluid cell contents; (c) When present over long periods of time the deleterious effects of tissue and plasma decomposition products and of bacterial products must be considered. There is much evidence which seems to support the theory that *toxemia* is an important lethal factor in burns, and Drinker and his associates have recently found experimentally that lymph collected from a burned area exerts a toxic effect when reinjected into the blood stream of either burned or normal patients.

This finding is of peculiar importance, for it provides evidence of the presence of a toxic substance which acts as a common etiological factor in lesions resulting from such apparently diverse and unrelated trauma as blast, burns, and crush, of the soft tissues.

Of all of these four types of trauma the greatest loss of plasma from the circulation occurs in burns, and up to the present time there is no perfect substitute for its replacement. Whole blood does not provide the amount of plasma lost without dangerously increasing the red blood cell concentra-

tion already existing. On the other hand the injection of large amounts of solutions of crystalloids will further increase the loss of plasma by washing it out of the blood stream through the patient's capillary walls, through which this less viscid solution will pass far more freely than will plasma.

Naturally the need for plasma will be governed by its loss, and a simple and accurate method for obtaining this is very desirable. Most of those suggested obtain averages only and are so graded that no harm will result, but all such average formulas fail to provide for the variations which are so frequent in the individual patient.

We admit that the original formula proposed by us is complicated, but by means of a graph recently prepared by Dr. Wolff this difficulty can be overcome so that it should be possible for every surgeon to estimate the total quantity of plasma remaining in the circulating blood in c c or expressed in grams of protein.

A CHART OF PROTEIN DEFICITS AFTER BURNS

In order to simplify the calculation of protein losses resulting from severe burns, values were calculated from the authors' equation for the average adult with a normal hematocrit reading of 45 per cent cells, and a body weight of 70 kg (154 lb). The calculated protein deficit, in grams, was plotted against the assumed hematocrit values for several plasma protein levels as shown in chart 1. Hematocrit values are represented by points on the horizontal base line, plasma protein deficits or equivalent plasma volumes by points on the vertical margins, and plasma protein concentrations by the curves. Therefore, each vertical line in the chart represents a given hematocrit value and each horizontal line a plasma deficit. To read the deficit for a burned patient, take the point at which the vertical line corresponding to the observed hematocrit value intersects the curve corresponding to the estimated plasma protein level, interpolating whenever necessary. The horizontal line from this point to the left margin of the chart indicates the plasma protein deficit in grams, and to the right the equivalent volume of normal plasma. If the weight of the patient differs markedly from 70 kg, for which the calculations were made, the deficit read from the chart must be multiplied by a suitable factor. An example is given on the chart. If only the hematocrit value can be determined, the protein level is assumed as 6.0 to 7.0 gm/100 c c during the first 48 hours following the burn, provided the total intake of fluids is restricted to three liters per day. It should be pointed out that large errors may be introduced if the protein level is unknown. In the uncontrolled burn case the protein level may vary between wide limits.

Hemoglobin levels equivalent to each hematocrit value may be substituted on the horizontal axis. This can be done because the chart defines the relationship of hemoconcentration to plasma protein loss caused by severe burns. The chart, however, cannot be used directly for burned cases complicated by hemorrhage, anemia or polycythemia. The anemic individual,

CALCULATED PLASMA PROTEIN DEFICIT IN SEVERE BURNS

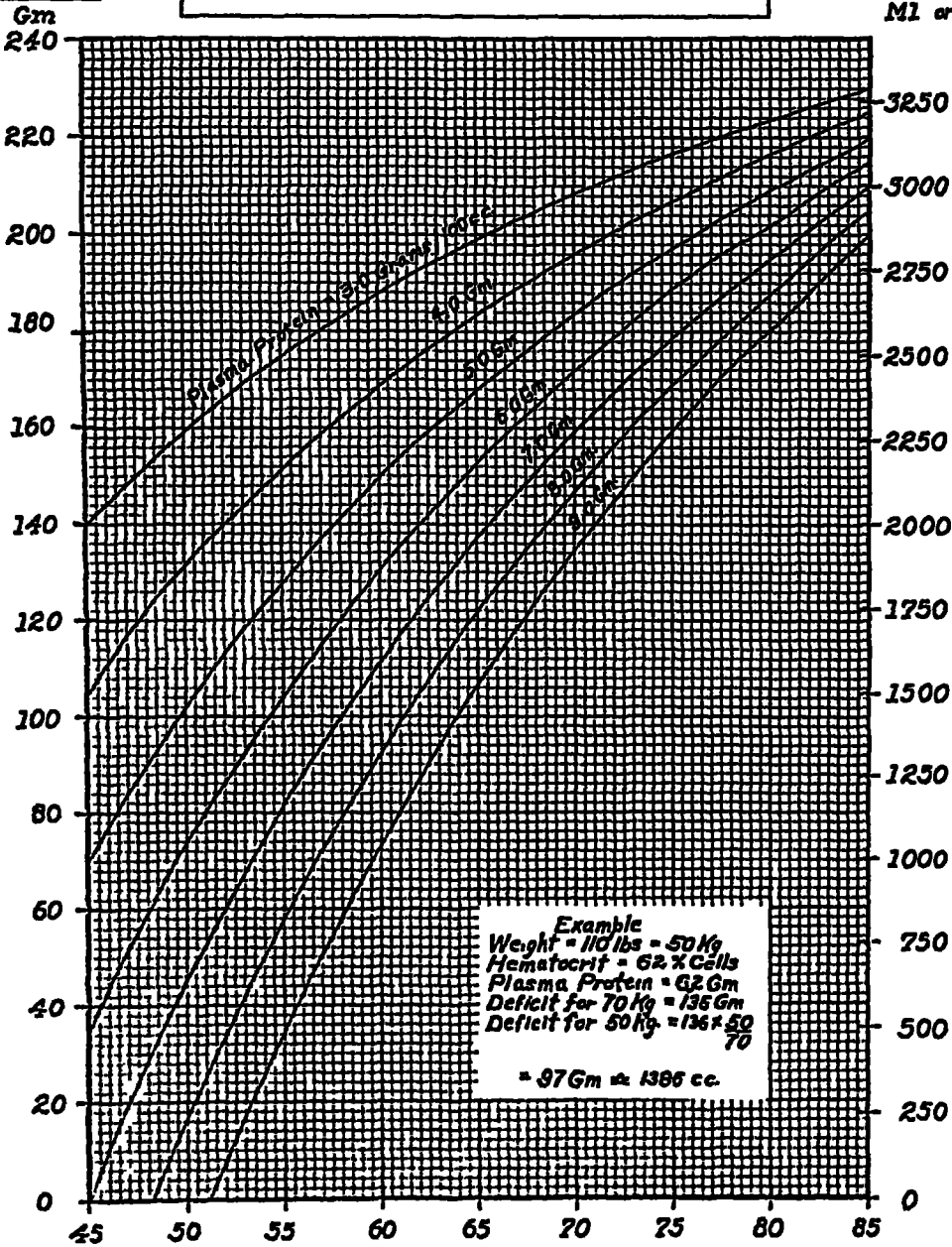
PRINTED IN U S A COPYRIGHT ANNALS of SURGERY J B LIPPINCOTT CO., PHILA., PA

$$\text{Grams Protein} = 3.5 W \frac{W(100-H_o)H_n P_o}{2(100-H_n)H_o}$$

$W = 70 \text{ Kg, Body Weight}$
 $H_n = 45 \% \text{ Cells, Hematocrit}$
 $H_o = \% \text{ Cells Shown in Graph}$
 $P_o = \text{Protein Levels Shown in Graph}$

PLASMA PROTEIN
DEFICIT

DEFICIT as VOLUME
NORMAL PLASMA
Ml or Cc



Ho = OBSERVED HEMATOCRIT

CHART 1

especially a child, presents a problem not easily handled by any chart or fixed rules. A whole series of charts, one for each basal hematocrit value, is needed for the entire range of anemias. The chart may be used if due allowances are made for the degree of anemia. At the same hematocrit level the plasma deficit for an anemic individual is 20 to 100 per cent greater than that for a person with a normal hematocrit reading. Therefore, values from the chart are minimal and must be increased proportionally for the anemic patient. This is also true for the burned patient who has lost red cells by hemorrhage. In the patient with polycythemia the protein deficit is considerably less than the value indicated by the chart. Allowances must be made for added red cells if a whole-blood transfusion is given. In all of these instances the most dependable value for the protein deficit is obtained by substituting probable normals in the formula and then calculating.

Crush Injuries. That there is a relationship—etiologic at least—between the syndrome following crush injuries and those following burns and blast, seems to have been definitely demonstrated, experimentally by Blalock. These three forms of trauma have in common the loss of plasma and the absorption of toxic products resulting from degenerative changes in the tissue cells, and plasma and from bacteria.

Several articles appeared in the German literature before and during the First World War recognizing the tissue effects of crush or compression injuries. It would seem to be chiefly expressed in peculiar renal lesions. This possibility appears to have escaped attention until recently—specifically following air raids upon the British Isles, in persons who have been trapped beneath falling debris. The ischemic muscle, the edema and swelling of the extremities as a result of transudation or escape of plasma, followed by concentration of the blood and terminating in oliguria and uremia expresses a similarity to the phenomena associated with blast and burn injuries. Blalock has been able to produce this condition experimentally in animals by crushing the extremities with a press which exerts a pressure of approximately 500 pounds per square inch. Although there was no immediate change in the general condition of the animal while the press was in action, marked changes occurred within 15 to 30 minutes after its removal. Though they have been unable to reproduce completely the clinical symptoms of the crush syndrome as exhibited by human patients, they do feel that they have evidence at hand that the prolonged ischemia of the extremities which was produced and maintained distal to these pressure points will ultimately end in massive death of tissue. If the presses are removed at the end of five hours and before actual death takes place, there follows an immediate flooding of the general circulation with metabolic products from the ischemic extremity which are probably in some ways similar to the substances of degeneration in the decomposing tissues and plasma and bacterial products of burns and blast and trauma of the soft tissues. Blalock feels it is quite possible that the burn syndrome holds an intermediate position between that of

the trauma alone as in blast of the soft tissues and to the trauma and ischemia which is superimposed in the crush type of wound

To summarize these four types of injury which are frequently encountered in warfare, the type of the regional and general fluid loss from the general circulation is a constant factor, but the extent may be variable. In addition to this, the degenerative changes of the dead and dying tissue cells, extravasated plasma and the results of bacterial growth and death are to be accepted also as a cause of the toxemia which clinically is found in all three conditions although with varying degrees of severity

35 MM. FILMS IN DIAGNOSIS OF CHEST CONDITIONS *

By EDMUND C. BOOTS, M.D., F.A.C.P., *Pittsburgh, Pennsylvania*

THE School Health Service Department of the Pittsburgh public schools serves approximately 130,000 children. When only those children were roentgen-rayed who showed enough abnormality to arouse suspicion on observation or physical examination, the standard 14 by 17 film method was sufficient to handle the volume of work.

Two years ago it was decided to make tuberculin testing and roentgen-ray examination of all positive reactors compulsory for all competitive inter-scholastic athletes and ninth grade pupils. When this was done, demand arose for the testing and roentgenological examination of the remainder of the student body whose parents were desirous of having the procedure carried out. As a result of this program, we have tested approximately 40,000 children, have taken 8000 roentgen-rays, and found 44 clinically active cases.

With our limited facilities and personnel, this volume of work could not be done with the standard 14 by 17 films. Therefore, we investigated, observed, and chose the 35 mm method. We have a 200 milliamperere machine and the fluorophotographic attachment using the 35 mm film. We do not have the services of a roentgen-ray technician.

We use 150 millamperes, a target distance of four feet, one-tenth second exposure, and vary the kilovoltage according to thickness and type of chest. We have found that it is necessary to give a higher kilovoltage than is indicated on the chart scales furnished with our machine. As the tube ages, these figures have to be increased.

It is our experience that the operator's technic must be more exact with the 35 mm attachment than with the 14 by 17 films. When a correct technic is secured, the films obtained show as good definition of structure as is obtained with the standard method. In reading these films, they may be mounted individually or read in a roll as we do as a time saving procedure.

A magnifying mechanism is necessary for the reading and several types are in use. There is one view box for use in stereo films, and another projector apparatus which enlarges the image on a screen so that several observers may view the picture at the same time and a pointer can be directed to the image of any desired shadow. We use the direct view box for the roll of flat films, because of the press of time. It is most satisfactory and does not distort the picture. We retake about 4 per cent of the films on 14 by 17 films for conference purposes.

One word of warning because of the sharpness of detail, abnormalities stand out like a sore thumb when the proper technic has been developed. A

* Presented before the Fifth Annual Regional Meeting of the American College of Physicians, Philadelphia, Pennsylvania, October 23, 1942.

man not accustomed to reading 35 mm film is prone to "over read" his films

This method finds its place where large numbers of films must be taken daily. It is not applicable where only a dozen or so chests are roentgen-rayed in the course of a day. It is of value where film storage space is at a premium. We have 8000 films stored for reference in a space approximately the size of an ordinary file drawer.

This method is recommended for mass survey work. A single film costs less than four cents, a 14 by 17 film would cost 65¢. Using 35 mm film enables us to take pictures in approximately one-tenth the time and at one-tenth the cost.

The measurement of the cardiac silhouette can be made on these films quite satisfactorily.

We are very well satisfied with this procedure. It has served our purpose well.

ACUTE NEPHRITIS AND THE EFFECT OF SULFONAMIDES ON THE KIDNEYS *

By FRANCIS D. MURPHY, M.D., F.A.C.P., and WILBUR D. WOOD, M.D.,
Milwaukee, Wisconsin

THE sulfonamides in their relation to the kidney may play the rôle of the "double-edged sword." They may participate in curing acute glomerulonephritis, or pyelitis, or they may harm the kidneys. Renal damage is considered the most important of the serious complications of sulfonamide therapy. It may result either from obstruction caused by masses of sulfonamide crystals in the renal tubules or ureters, or from parenchymal changes due to the nephrotoxic action of these drugs. Many reports have been published regarding the mechanical blocking of the tubules, pelvis and ureters, and the hematuria, oliguria, anuria and uremia which may follow the blocking have been carefully studied^{1, 2, 3, 4, 5, 6}. Reports of the nephrotoxic action of sulfonamides have been less common, but it is not improbable that many milder forms of renal damage of this kind have passed unrecognized or, at least unreported. Enough evidence has been obtained to show that some patients may develop pathologic changes of the kidney in the absence of mechanical obstruction^{1, 4, 7, 8, 9, 10}. In some instances both kinds of injury may be found in the same kidney.

The beneficial effects of the sulfonamides in the treatment of acute nephritis are not well known, because of the prevalent fear lest these drugs aggravate the injury of an already diseased kidney. It is known, however, that sulfanilamide is excreted almost entirely in its free form by the kidney, and that the crystals of the acetylated form are not found, as they are with sulfapyridine, sulfathiazole, and sulfadiazine. The report by Williams, Longcope and Janeway¹¹ suggests that sulfanilamide may play an important rôle in the treatment of acute glomerulonephritis. These authors believe that sulfanilamide may attack the foci of infection which support the activity of nephritis. They found no instance of any injury to the kidney due to sulfanilamide. The use of sulfapyridine, sulfathiazole, and sulfadiazine presents a somewhat different problem because of the insolubility of the acetylated forms of the drug, which are excreted by the kidney and which may cause mechanical interference with renal function.

Observations on Benefits from Sulfonamides in Treating Patients Who Have Acute Glomerulonephritis. Our experience with sulfonamides and acute nephritis has been limited to observations on patients who had other diseases than nephritis which called for sulfonamide therapy. In this group

* Read at the Regional Meeting of the American College of Physicians in Chicago, November 21, 1942.

From the Department of Medicine, Marquette University School of Medicine, and the Medical Clinics, Milwaukee County General Hospital, Milwaukee, Wisconsin.

there were three cases of acute nephritis in which the sulfonamides not only were not harmful, but were beneficial. One of these cases will be reported in some detail, as it is illustrative of our experiences with this group.

Of the three cases, one was a patient with an acute glomerulonephritis resulting from an acute streptococcal sore throat. The nephritis cleared up after giving sulfanilamide for a period of one month by the method usually employed in the administration of this drug. The second case was one of acute lobar pneumonia with an exacerbation of a latent glomerulonephritis. Sulfadiazine was given according to the usual methods. The acute nephritis was not made worse, but improved, and although complete healing of the kidney did not follow, the nephritis again became latent. The third case is the best example of the group and will be given in more detail.

CASE REPORT

A 12 year old boy was admitted to the hospital on September 7, 1942 because of fever, vomiting, puffiness of the entire body, and shortness of breath. The boy had been in good health up to four days prior to admission, when chills, fever, and vomiting developed abruptly.

Physical Examination The physical examination revealed a dyspneic, flushed boy with a fever of 105° F. The pulse was rapid, and the apex beat was slightly displaced to the left. There was a lobar pneumonia involving the right lung. Blood pressure was 150 mm Hg systolic and 110 mm diastolic. The leukocyte count was 18,500 with 48 per cent nonsegmented neutrophilic cells.

Urinalysis The specific gravity was 1.014. Albumin, four plus. There were many granular casts, 8 to 10 red blood cells and many pus cells per high power field. The urinary output during the first 24 hours was 450 c c.

The non-protein nitrogen was 68 mg per cent.

Treatment Two grams of sulfathiazole were given at once, and 1 gram every four hours thereafter for seven days. The sulfathiazole level in the blood ranged during the course of the pneumonia from 8 to 11 mg per cent. In eight days the pneumonia was brought under control. The leukocyte count and fever dropped almost to normal and the patient was greatly improved. The glomerulonephritis was not intensified, on the other hand, it had subsided somewhat. One gram of sulfathiazole was then given every eight hours for the next five days. The fever at this time began to rise again, and further examinations and roentgenogram of the chest showed the beginning of an empyema. Fluid was removed from the chest and pneumococci were demonstrated in culture. Shortly afterwards closed drainage was established. Sulfathiazole was administered in 1 gram doses every eight hours, and the blood level was maintained between 4 and 8 mg per cent. The treatment of the empyema and nephritis was continued for six weeks during which time the empyema was cured and the nephritis improved, though it was still active. The patient was treated with sulfathiazole in 1 gram doses every eight hours for another six weeks, and by the end of this period the glomerulonephritis had completely healed.

Summary of Case A boy, 12 years old, developed pneumonia and acute glomerulonephritis in early September, 1942. With the usual doses of sulfathiazole, the pneumonia was controlled in eight days. The acute nephritis was not made worse, but showed some improvement. Subsequently empyema developed. Sulfathiazole was continued along with other treat-

ment for a period of six weeks. The empyema was cured and the acute nephritis made much better. Sulfathiazole was given for the treatment of the acute nephritis for another six weeks, and during this period the acute nephritis was completely cured.

The Nephrotic Action of Sulfathiazole The insoluble, acetylated forms of sulfathiazole may produce blocking of the urinary passages followed by albuminuria, hematuria, pain, oliguria, anuria, and uremia. Of the kidney injuries caused by the sulfonamides, this is the commonest, but there is another type of kidney damage that is not characterized by obstructive lesions. By some process not entirely clear, the sulfonamides may impair kidney function by action particularly upon the kidney tubules. Postmortem examinations have disclosed that the glomerular tufts are not involved, and that obstruction by sulfonamide crystals is not the cause. The following is a case that exemplifies renal damage followed by oliguria, anuria, uremia and death caused by sulfathiazole, without evidence of urinary tract blockage at any point.

CASE REPORT

A white woman, aged 64, developed an upper respiratory tract infection for which the physician who saw her at home gave 1 gram of sulfathiazole every six hours until 8 gm in all were given. While at home she developed oliguria. Sulfathiazole was stopped and she was brought to the hospital where she was seen by us for the first time.

The patient was a well developed woman who was in a precomatose state and greatly dehydrated. Many râles were heard throughout both lungs, but otherwise her respiratory system was normal. The output of urine which had been scanty at home, diminished at the hospital, and diuresis failed to take place even though large quantities of fluids and other treatments were given. Urinalysis showed albumin four plus, many red blood cells, very many pus cells, and a few granular casts. The fever was remittent in type and ranged from 99° to 101° F. Blood pressure was 148 mm Hg systolic and 100 mm diastolic. The average blood counts showed White blood cells, 8,500, differential count normal, red blood cells, 3,650,000, hemoglobin, 55 per cent. The non-protein nitrogen and creatinine gradually rose despite usual treatment. Urological examination revealed no urinary tract obstruction. She died of uremia nine days after entrance to the hospital.

Autopsy The heart showed nothing abnormal for a patient in her age group.

The lungs were congested but no pneumonic consolidation was found. The bronchi contained grayish-green mucoid material, and on microscopic examination, the smaller bronchi were surrounded in places by areas of polymorphonuclear infiltration. The bronchioles in some areas were occluded by a semifibrinous material.

Hemorrhagic gastritis and colitis were present.

The right kidney weighed 190 gm, the left 185 gm. There were no specific lesions in the pelvis or ureters and no calculi or clumps of crystals were seen. The capsules stripped with ease and the surface of both kidneys was smooth and pale. On cut surface, the cortex was red and stood out in sharp relief against the grayish, anemic appearing medullary portion.

Microscopic Examination On histological examination the glomerular capillaries were congested. The Bowman's capsules seemed normal. The epithelial cells of the convoluted tubules, particularly the distal portions, were swollen, and in places degenerated and undergoing necrosis, some of the tubular lumina appeared occluded by

epithelial cells The collecting tubules contained brownish material which appeared to obstruct them in places Throughout the medullary portion and to some degree in the cortex small foci of lymphocytic infiltration were found Examination for sulfathiazole crystals was made, and many were found in the mucosa of the pelvis of both kidneys The kidney picture was not unlike that seen in nephrosis of the chemical kind

Remarks This case illustrates several lessons on sulfonamide therapy First, the promiscuous giving of sulfonamides for comparatively innocent upper respiratory tract infections should be avoided Secondly, in administering these drugs, the precautions which have been emphasized by those most experienced in their use should be adhered to For example, in this case the patient was in a state of marked dehydration, and it might have been possible to safeguard the kidneys if an optimal amount of fluid had been given each day with the drug Thirdly, this case shows that in certain individuals even small doses of sulfathiazole may lead to unfavorable reactions Finally it must be kept in mind that sulfonamides may not only cause a mechanical obstruction of the urinary tract, but they may exert a more direct nephrotoxic action on the renal parenchyma followed by oliguria, anuria and uremia

Prophylaxis and the Effect of the pH of Urine on the Formation of Crystals An encouraging feature of most of the reports on kidney injuries from sulfonamide therapy is the confidence which writers place in satisfactory methods for their prevention and control^{1, 12, 14} There are probably several factors which are concerned in the genesis of renal damage from administration of sulfonamide compounds Safeguarding the kidney may be achieved by the following precautions (1) An adequate intake of fluid, the hydration of the patient's tissues, and a normal output of urine are probably the most important measures for avoiding kidney injury General opinion is that 1500 to 2000 cc of fluid per day must be taken if adequate urinary output is to be assured (2) The presence of renal insufficiency or of obstructive uropathies must be evaluated before commencing sulfonamide therapy (3) Careful observations of the quantity of urine and its appearance on gross examination and the microscopic examination for crystals should be made The presence of sulfonamide crystals does not mean that kidney damage is at hand and that the drug must be stopped, but it does indicate that much care must be exercised concerning the quantity of the drug given, the optimal level in the blood stream and the volume of urine excreted (4) Finally several investigators have spoken of the importance of an alkaline urine in the prevention of crystal formation^{1, 7, 17, 18, 16} This idea is not held by all observers, and Thompson, Herrell and Brown,² and Finland, Peterson and Goodwin,¹⁰ do not stress the rôles of alkalinity and acidity in the precipitation of crystals in the kidney

It had become our general impression that when the pH of the urine was kept well on the alkaline side, sulfonamide crystals were diminished in the urine In order to corroborate this opinion, 50 patients were selected at

CHART I

Relation of pH of Urine to Crystalluria from Sulfadiazine Therapy

Group 1 pH 4-5			Group 2 pH 5-6			Group 3 pH 6-7			Group 4 pH 7 and over		
pH	Crystals	Blood Levels of Free and Acetylated Drug	pH	Crystals	Blood Levels of Free and Acetylated Drug	pH	Crystals	Blood Levels of Free and Acetylated Drug	pH	Crystals	Blood Levels of Free and Acetylated Drug
4.8	0	(F) 8.9	5.4	0	(F) 10.5 (A) 1.7	6.0	++	(F) 14.7 (A) 1.2	7.0	++	
4.8	0		5.0	++	(F) 12.8 (A) 0.82	6.0	+	(F) 14.7 (A) 1.2	7.2	+	
4.9	0	(F) 7.7	5.3	+	(F) 9.6 (A) 2.5	6.4	0	(F) 8.1 (A) 3.2	7.0	0	(F) 5.9 (A) 2.0
4.9	+++		5.3	0	(F) 15.0 (A) 1.36	6.1	0	(F) 8.7 (A) 0.8	7.9	0	(F) 9.6 (A) 1.9
4.9	0		5.8	0	(F) 18.2 (A) 2.6	6.1	0	(F) 10.9	7.5	0	(F) 14.09 (A) 3.5
4.8	0		5.0	+	(F) 11.2 (A) 0.68	6.0	0	(F) 11.75 (A) 1.2	8.6	0	(F) 14.1 (A) 2.8
4.9	+		5.6	+	(F) 10.2 (A) 1.8	6.3	++	(F) 11.9 (A) 0.6	8.2	0	(F) 6.4 (A) 0.6
4.8	++++	(F) 10.2 (A) 0.7	5.1	++	(F) 11.0 (A) 0.8	6.5	+	(F) 12.8 (A) 1.2	7.7	0	(F) 9.5
4.9	++++	(F) 8.1 (A) 1.4	5.5	+	(F) 8.9 (A) 3.6	6.0	++	(F) 11.2 (A) 1.6	7.6	0	(F) 16.3 (A) 3.3
4.9	++++		5.2	+	(F) 13.1 (A) 3.3	6.2	0	(F) 14.6 (A) 0.9	7.6	0	(F) 13.0 (A) 3.0
4.9	+	(F) 8.9 (A) 3.5	5.3	+	(F) 6.3 (A) 1.0	6.7	0	(F) 9.8 (A) 1.5	7.5	0	(F) 12.6
4.8	++++	(F) 7.8	5.3	++++	(F) 8.4 (A) 0.6	6.4	+	(F) 7.8 (A) 1.7	7.6	0	(F) 11.31 (A) 1.3
4.3	+	(F) 8.3 (A) 1.3	5.4	0	(F) 8.1 (A) 0.7	6.0	++++	(F) 10.3 (A) 3.4	7.7	0	(F) 6.9 (A) 2.06
4.8	+		5.4	++++	(F) 9.9 (A) 3.6	6.0	++	(F) 14.5 (A) 2.2	7.0	+	(F) 9.6 (A) 1.2

F—Free drug

A—Acetylated form of drug

In group 1 there were 14 urinalyses taken in all, in group 2 there were 88, in group 3, 88 and in group 4, 43. The figures given above are typical of the trend of crystalluria in relation to pH. Averages taken for each group show that alkalinity probably has an effect on the crystalluria. The averages of the crystalluria in each of the 4 groups are as follows: (a) In group 1 with a pH of 4-5, the average number of crystals was 1.642; (b) In group 2, pH 5-6, it was 1.25; (c) In group 3, pH 6-7, the incidence of crystals was 1.022; (d) and in group 4, pH of 7 and over, the average number of crystals was only 0.232.

random and placed on 1 gram of sulfadiazine every four hours. Most of these patients were relatively young and were not afflicted with any kidney or liver disease. Specimens of urine were taken each morning at 10 o'clock and examined within 20 minutes for crystals. The urine was made alkaline by giving soda bicarbonate 1 gram with each gram of the sulfadiazine. The fluid intake was maintained at 2500 c c a day, and levels of the free and acetylated drug in the blood were determined every other day. From the findings given in chart 1, it seems that in alkaline urines fewer crystals were found than in those with an acid reaction.

SUMMARY

1 Sulfonamides may in some cases cure acute glomerulonephritis, and other acute inflammatory lesions of the kidneys, but under certain circumstances they may cause kidney damage.

2 Two cases of nephritis benefited by sulfonamide therapy are mentioned and a third case described more fully in which treatment with sulfathiazole resulted in complete recovery.

3 A case illustrative of the nephrotoxic action of sulfathiazole is given, and the findings at autopsy are reported.

4 Precautionary measures which have proved their value in cases treated with the sulfonamides are outlined.

5 There is no unanimity of opinion concerning the rôle of alkalinization in preventing crystalluria. A preliminary report of our observations on this question is included. It appears that alkalinity may diminish the incidence of crystalluria.

BIBLIOGRAPHY

- 1 WINSOR, T, and BURCH, G E. Renal complications following sulfathiazole therapy, Jr Am Med Assoc, 1942, cxviii, 1346.
- 2 THOMPSON, G J, HERRILL, W E, and BROWN, A E. Anuria after sulfadiazine therapy, Proc. Staff Meet Mayo Clin, 1941, xvi, 609.
- 3 SCHULTZ, J W, SHIDLER, F P, and NIEBAUER, J J. Acute urinary suppression following sulfadiazine therapy, Jr Am Med Assoc, 1942, cxix, 411.
- 4 BRADFORD, H A, and SHAFFER, J H. Renal changes in a case of sulfadiazine anuria, Jr Am Med Assoc, 1942, cxix, 316.
- 5 LEDERER, M, and ROSENBLATT, P. Death during sulfathiazole therapy, Jr Am Med Assoc, 1942, cxix, 8.
- 6 KEITZER, W A, and CAMPBELL, J A. Renal complications of sulfadiazine, Jr Am Med Assoc, 1942, cxix, 701.
- 7 MERKEL, W C, and CRAWFORD, R C. Pathologic lesions produced by sulfathiazole—report of 4 fatal cases, Jr Am Med Assoc, 1942, cxix, 770.
- 8 CUTTS, M, BUGGESS, A M, and CHAFFE, F H. Treatment of lobar pneumonia with sulfathiazole and sulfapyridine, New England Jr Med, 1940, ccxxiii, 762.
- 9 FISHER, A M. The use of sulfonamides in renal insufficiency, Jr Mt Sinai Hosp, 1942, viii, 509.
- 10 FINLAND, M, PETERSON, O L, and GOODWIN, R A, JR. Sulfadiazine: further clinical studies of its efficacy and toxic effects in 460 patients, ANN INT MED, 1942, xii, 920.

- 11 WILLIAMS, R H, LONGCOFF, W T, and JANEWAY, C A The use of sulfanilamide in the treatment of acute glomerulonephritis, *Am Jr Med Sci*, 1942, cciii, 6
- 12 LONG, P H The toxic manifestations of sulfonamide therapy, *Connecticut State Med Jr*, 1943, vii, 6
- 13 FINLAND, M, STRAUSS, E, and PETERSON, O L Sulfadiazine therapeutic evaluation and toxic effects on 446 patients, *Jr Am Med Assoc*, 1941, cxvi, 2641
- 14 LEFDHIM-GREEN, J C Renal complications of sulfapyridine, *Brit. Med Jr*, 1941, ii, 586
- 15 SCHWARTZ, L, FLIPPIN, H F, REINHOLD, J G, and DOWN, A H The effect of alkali on crystalluria from sulfathiazole and sulfadiazine, *Jr Am Med Assoc*, 1941, cxvii, 514
- 16 CURTIS, A C, and SOBIN, S S The solubility of acetylsulfapyridine and acetylsulfathiazole in the urine, *ANN INT MED*, 1941, xv, 884

MEDICAL ASPECTS OF HIGH ALTITUDE FLIGHT *

By DAVID N W GRANT, Brigadier General, AUS, The Air Surgeon,
Washington, D C

SINCE civilization moved north from the warm climates of the south-eastern Mediterranean, man has been required to devote some part of his energies to adjusting himself to his physical environment. Historians wish to emphasize that man's migration into new environments is but an expression of progress, and tell us that the restless spirit finds its greatest examples among the hearty of a race who seek "new worlds to conquer." Be that as it may, certainly in recent times many men have not been content with conquering the surface of the earth, but have directed their energies to mastering that which is below and above the surface of the earth.

The history of man shows that he has been ever seeking new means of transportation for the purpose of increasing his speed and for exploring beyond his environment, and each new development in transportation has brought with it its own peculiar medical problems. Travel by water brought with it drowning; the subjugation of animals, fractures of various kinds, the development of the steam engine, the so-called "railroad spine"; the gasoline engine, carbon monoxide poisoning, and with the automobile, the typical Colles fracture. And now we have the air plane with its tremendous speeds, in three dimensions, which introduces entirely new medical problems, as man is now placed in an environment in which he is not naturally adjusted to live. From the time he leaves the ground until he returns, he is living under unnatural conditions. In attaining altitude and traveling at such tremendous speeds he is defying nature.

Some 20 years ago it was realized by a few individuals that the performance of the aeroplane was limited only by the performance of man in this strange environment in which he found himself. The pilot of the aeroplane is the heart and brains of the machine. The machine may be defective, but the pilot brings it to earth. But when the pilot fails only momentarily, no matter how well the machine is functioning, there is no direction to the flight and it crashes. And so to insure the proper functioning of man in this new and strange environment, Aviation Medicine was born, and with it the Flight Surgeon.

We who are intimately connected with Aviation Medicine like to visualize the Flight Surgeon as having the same relation to flying personnel as the engineer has to flying matériel. The engineer assures himself that the machine is functioning perfectly before he allows it to take off into the air. The Flight Surgeon assures himself that the personnel who are to operate the machine will function perfectly.

* Delivered before the New England Regional Meeting of the American College of Physicians, Boston, Mass., February 5, 1943.

With these preliminary remarks, I would like to call to your attention a few of the medical problems involved in aviation. Aviation, as we know it, involves two big factors: first, the development of the mechanical means of making flight possible, and secondly, the adjusting of the operators or occupants of this mechanical means to the conditions they will face in the environment into which they will be carried.

In regard to the first factor, suffice it to say that the development of the aeroplane has outstripped the development of our knowledge of human beings under conditions of flight. The situation would not be so tragic if aeroplanes were used solely for commercial purposes, but military needs and uses demand high-altitude flying, dive-bombing operations and rapid maneuvering where judgment, split-second reactions, and the effects of acceleration and anoxia are determining factors. Inasmuch as we have not been able to develop a superior race or immunize our flying personnel from the precariousness of operational flying, future gains in flying will of necessity have to be made through advancements in knowledge of physiology and allied subjects.

I would like to outline briefly a few of the main problems in Aviation Medicine with which we are concerned. I will restrict my remarks to five major problems, and give them in the order of their importance:

- 1 Selection and training of flying personnel
- 2 Anoxia or oxygen-want
- 3 Aero-embolism
- 4 Expansion of gases in the body cavity and alimentary canal
- 5 Low temperatures

It is interesting to note in passing that in the development of aero-medicine, these problems appeared historically about in their present order of importance, and each has been greatly emphasized by the present war. It was my interesting experience to visit England after the battle of Britain to study the findings of the R A F, and I have now just returned from Africa. I believe that much of the mastery of the air in the battle areas is dependent upon solving these problems.

Selection and Training of Flying Personnel During the early days of aviation, the selection and training of flying personnel were predominantly on the basis of trial and error, or survival of the fittest. Personnel was not selected because of any peculiar fitness for flying—it was simply a question of whether the individual had the nerve to fly. The result was that the average aviator had a very short time of usefulness. Little by little the physical and mental requirements for entering flying training have been raised, and with the newer methods of selection of trainees, we are speedily removing that costly procedure of survival of the fittest. An extensive program has been established not only to select those aviation cadets who are best qualified to receive flying training, but also to select those for further specialized training and assignment to high altitude operations. Thus high

altitude training also adequately indoctrinates all members of the air crew in the general subject of high altitude flying. The aero-physician has played a large part in the establishment of this program, and at the present time we have two large research centers and many additional research activities working toward the solution of this problem. The preparation of the flight crew has been almost entirely a duty of the flight surgeon who examines, instructs, and frequently flies with his men. Because of the fact that the selection and training of flying personnel is a separate subject unto itself, I do not believe that it would be wise to do more than to bring it to your attention now. Therefore, I will pass on to the second heading.

Anoxia or Oxygen-Want Aviation medicine requires knowledge of many physical principles which are intimately connected with problems presented in this talk. The question of anoxemia is an excellent example of this. The decrease in barometric pressure which occurs as one ascends to greater and greater altitudes restricts the level to which one can fly without supplemental oxygen, and even the level to which one can fly breathing 100 per cent oxygen. This latter ceiling, as determined experimentally, is approximately 40 to 42,000 feet. Beyond this, pressure cabins or pressure suits must be used. One of our major problems has been that of designing a satisfactory oxygen mask. Our mask today only basically resembles that which we used two years ago. Even were this aspect of the question successfully solved, there remains the fundamental problem of the effect of chronic anoxia upon flying personnel. Although we know that oxygen-want does not have the same effect upon all individuals, we believe that it is mandatory that everyone use oxygen equipment above 10,000 feet, in the event that flight is to be longer than two hours. The individual should never exceed 15,000 feet even momentarily without oxygen, in spite of the fact that he is relatively inactive and has no obvious symptoms. Provided there is a need for a peculiar mental or physical exertion, oxygen should be taken at a lower altitude. The average individual begins to become anoxic at altitudes above 33,000 feet, even though he is breathing 100 per cent oxygen and is engaging in little or no activity. This anoxemia becomes progressively greater with increased altitude. Although it is theoretically possible for a normal individual to ascend to altitudes of about 46,000 feet, it is felt that for military purposes the maximum that should be demanded is 42,000 feet. As a matter of fact, from a medical standpoint, it is desirable to use a pressure cabin for all altitudes above 30,000 feet. At altitudes as low as 4,000 feet, there is commonly a change in pulse rate and a slight rise in blood pressure, which shows a general rise to 8,000-12,000 feet, and then commonly begins to fall.

As a result of the work done by Schneider, it was found that there are two general types of reactors, "fainters" and "non-fainters," which are nearly equally divided. The fainting type are those in whom the lower nervous centers which control the heart rate, vascular tone and volume of

breathing, suffer paralysis before the higher or psychic centers are affected. This fainting type of reactor usually suffers a sudden reduction in his blood pressure at the time of fainting. This general type of fainting reaction should not be confused with the unconsciousness that occurs at high altitudes as a result of a sudden interruption in the oxygen supply system. It should be remembered that the higher the altitude, the shorter the time necessary to produce unconsciousness due to lack of oxygen.

Perhaps the most dramatic demonstration witnessed by research workers using the "altitude training" or "low pressure chamber" is the speed with which unconsciousness overtakes man at altitudes above 30,000 feet. At 35,000 feet without oxygen, unconsciousness will appear in 30 to 60 seconds, at 40,000 feet, in 15 seconds. Above these levels there is progressive acceleration in the appearance of unconsciousness.

Aeroembolism The rapid climbing abilities of modern airplanes have created a situation in which the body of the aviator is rapidly decompressed with danger of liberation of bubbles of gas, mainly nitrogen, from the blood and tissues. This condition in aviators corresponds to the compressed-air illness in deep-sea diving called the "bends." Aeroembolism is a condition caused by the same general process that causes compressed-air illness, with the exception that the former occurs from compression to two or more atmospheres followed by decompression, whereas the latter occurs from decompression from one atmosphere or less.

During ascent in aircraft or in any other situation in which the atmospheric pressure is decreased, the internal partial pressure of the body nitrogen is above that of the nitrogen in the lungs, and the tissues, therefore, are supersaturated. As a consequence, the nitrogen dissolved in the blood begins to be liberated in the lungs. The nitrogen in the tissues begins to enter the blood stream, and by this dual process the body tends to rid itself of its excess nitrogen. If the ascent is slow enough so that the nitrogen in the body can be eliminated before reaching approximately double its normal saturation at the prevailing altitude, nothing unusual will occur. If, on the other hand, concentrations of nitrogen in the body become more than double their normal saturation values at any altitude pressure, the nitrogen will tend to come out of solution and form bubbles.

Since the elimination of nitrogen from the body is entirely through the blood stream, those parts of the body or those tissues which have the poorest blood supply will be least able to lose their excess nitrogen rapidly. That this is actually correct is indicated by the fact that with rapidly decreased atmospheric pressure, these bubbles are found in the spinal fluid and about the spinal column at 18,000 feet, whereas bubbles in the blood and body tissues generally have not been found below 30,000 feet. This entirely agrees with the actual findings in flight where it is not unusual to have minor symptoms, such as itching and tingling sensations, a little above 18,000 feet. It is quite unusual, however, to have an individual incapacitated as a result of aeroembolism below 30,000 feet.

It is obvious that if one ascends slowly enough to high altitudes, the nitrogen of the body will be eliminated as fast as it tends to become excessive. Therefore, the rate of ascent is important since the nitrogen content of the tissue must reach a value at least twice normal at any given atmospheric pressure before it will appear as bubbles.

The calculated maximum rate of ascent which will avoid bubble formation is not more than 78 feet per minute. It is obvious that this rate will always be exceeded in aircraft, and therefore some other solution must be found.

A large amount of information is being accumulated on the preliminary use of oxygen to wash out excess nitrogen prior to take-off. It is known that breathing 100 per cent oxygen for one-half hour, while taking active exercise, will remove a certain amount of nitrogen and will make certain individuals more comfortable during rapid ascents. This procedure, of course, is quite impractical for defensive military operations, and there is still some question as to how much it contributes other than delaying the onset of aeroembolism.

The number of individuals who will be incapacitated at any given altitude is not precisely known. Certain individuals with no preliminary preparation are able to go to 40,000 feet, and above, repeatedly, for one to two hours with no symptoms, whereas others consistently have symptoms which are incapacitating at slightly above 30,000 feet. As a result of the English experience, it is probable that not over one-half of the young, healthy aviation cadets can go to 35,000 feet for four hours without symptoms.

Expansion of Gases in the Body Cavities and the Alimentary Canal Probably one of the most frequent difficulties experienced by flying personnel in flight is with reference to the middle ear. If for any reason the eustachian tube is closed, which may occur during a common cold, pharyngitis or sinusitis, the middle ear cannot be ventilated and a marked change of altitude may then rupture the eardrum. A like condition occurs in the case of the sinuses when their openings are blocked, in which case, during a change of altitude, marked trauma and severe pain may develop. The abdominal distention which occurs as a result of the expansion of gases in the gastrointestinal tract is often severe enough to incapacitate the individual, provided the rates of ascent are rapid.

Low Temperatures The problem of cold or low temperatures was intentionally placed last because it is primarily an engineering problem, and I understand that we are already well on the way to an adequate solution.

Other Subjects I would like to mention briefly high accelerations, fatigue, and clothing, as subjects which have intentionally been omitted from this discussion. Although these subjects are also important and may limit high altitude flights, they are in no way peculiar to such operations and are entirely secondary to the subjects discussed above. The problem of high accelerations will be a greater problem for low-flying aircraft. Fatigue is

not limited to high altitude, although there is considerable evidence that it does develop more rapidly under such conditions. Clothing, although important, is again not a satisfactory answer to the cold problem. Clothing, in general, is entirely inadequate for continued operations if the temperatures are below 10° F.

There is perhaps no one problem of greater importance to the winning of this war than that of the proper application of aviation medicine. It finds its way into every air activity—transport, reconnaissance, and fighting. The reports that I have of recent endeavors toward solving our problems are extremely encouraging. Much work is yet to be done, but American ingenuity and American medical research will solve it.

THE PRESENT STATUS OF CLINICAL ELECTROENCEPHALOGRAPHY *

By FREDERIC A GIBBS, M D , *Boston, Massachusetts*

AFTER eight years of trial, clinical electroencephalography has gained widespread acceptance. It is being used by neurologists, brain surgeons, psychiatrists, and pediatricians, as an aid in the diagnosis of epilepsy and related disorders and as a painless and entirely safe method of detecting localized damage in the cerebral cortex. Several Army induction centers are using it as part of the medical examination to determine fitness for military service.

This widespread acceptance has placed a burden on electroencephalographic standards for diagnosis and prognosis, and various weaknesses have appeared. In the effort to correct these weaknesses, electroencephalographers in this country and abroad are collecting large numbers of electroencephalograms on normal and abnormal persons at various age levels so that standards can be given a solid statistical basis. Such studies could not be done at an earlier stage because, like most new sciences, electroencephalography in its beginnings was descriptive. Single cases or small groups yielded essential information that revealed the general shape of the field, and provided clues to the directions in which large scale studies could profitably proceed. However, the descriptive stage of clinical electroencephalography is now over, it is entering its quantitative, or statistical phase. This will seem to many a less interesting period, but only in this phase can electroencephalography be rationally applied, for until standards are based on large numbers of uniformly classified cases, electroencephalographic diagnosis will be unreliable.

The study of 1,000 normals and 1,200 epileptics¹ reveals that although some supposedly normal persons show abnormalities of the type encountered in epileptics, certain disorders are so common in epileptics and so rare in normals that they have diagnostic value. For example, the most characteristic type of disorder, namely, seizure-discharges, was observed in 30 per cent of the epileptics and in fewer than 1 per cent of the controls. A somewhat less extreme form of abnormality, very slow or very fast activity, occurred in 25 per cent of the epileptics and in only 2 per cent of the controls. The mildest form of abnormality, moderately slow or fast activity, was twice as common in the epileptics as in the controls. Only 15 per cent of the adult epileptics and 10 per cent of epileptic children were classified as normal, in contrast to 85 per cent classified as normal in the control group, but

* Read before the New England Regional Meeting of the American College of Physicians in Boston, Mass., February 5, 1943.

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital, Boston, Mass.

it is clear that a significant proportion of epileptics have normal electroencephalograms in their interseizure periods. Therefore, like a negative Wassermann, a "negative" electroencephalogram is only suggestive. For that matter, a "positive" electroencephalogram is only suggestive. However, it may be *highly* suggestive. The ratio of epileptics with seizure-discharges to normals with seizure-discharges is of the order of 30 to one, therefore, seizure-discharges can be considered confirmatory of epilepsy. Although less significant, very slow or very fast activity is suggestive of epilepsy and such a finding would strengthen a clinical diagnosis of epilepsy. The finding of moderately slow or fast activity is inconclusive, but it is entirely in accord with a clinical diagnosis of epilepsy. If a normal electroencephalogram is reported in a clinical epileptic, it is probably wise to reconsider the grounds on which the diagnosis was made, but if these are found to be satisfactory, there is no reason to doubt the diagnosis.

Much emphasis is placed on epilepsy because that is the condition which presents the widest range of electroencephalographic abnormalities. However, in brain trauma, very evident disturbances of the electroencephalogram are also encountered. Statistically significant data on this condition have been made available by the publication of Williams' study on 600 consecutive cases of head injury at the Military Hospital in Oxford.²

Other conditions in which electroencephalography has been found to be clinically useful are the following: cerebral tumor, subdural hematoma, cerebral hemorrhage, cerebral thrombosis, cerebral abscess, meningitis, encephalitis, Schilder's encephalomyelitis, Sydenham's chorea and behavior disorders. It has almost no clinical value in schizophrenia, manic-depressive psychosis, feeble-mindedness, migraine, psychoneurosis and hysteria.

Because so little abnormality is seen in feeble-mindedness or schizophrenia it is apparent that the electroencephalogram does not give a record of all brain activity. The electroencephalogram records one particular type of brain activity from a particular brain area, namely, the outer convexity of the hemispheres. The electroencephalogram can localize disorder in cortical areas that are otherwise silent, but it does not indicate the cause of the disorder. It supports or weakens a clinical diagnosis, but it does not make a clinical diagnosis. As a source of additional evidence, it may be extremely valuable but it cannot be regarded as a "time-saver."

The value of an electroencephalogram is directly proportional to the experience and ability of the electroencephalographer who makes and interprets it. The taking of satisfactory records requires training and more than common skill and diligence, and their interpretation requires inherent powers of discrimination. However, a primary requirement is that the electroencephalographer be equipped with a correctly designed and properly built instrument. It is impossible for a good man to obtain satisfactory results with a poor instrument, and an incompetent man with a poor instrument is a source of egregious error.

One of the surprising and encouraging aspects of medical practice in this country is the readiness with which innovation is accepted. New and highly technical diagnostic methods become standard procedures almost overnight. In a few more years the electroencephalograph will not be curious or wonderful, but only familiar and increasingly useful.

BIBLIOGRAPHY

- 1 GIBBS, E L, GIBBS, F A, and LENNON, W G. Electroencephalographic classification of epileptics and controls, Arch Neurol and Psychiat (In press)
- 2 WILLIAMS, D. The electro-encephalogram in chronic posttraumatic states, Jr Neurol and Psychiat, 1941, 11, 131-146

OBSERVATIONS ON IMMUNITY IN MUMPS *

By JOHN F ENDERS, PH D , *Boston, Massachusetts*

THE importance of the problems of the control and prevention of mumps among military personnel was illuminated by the events of the last war when nearly four million man days were lost from duty because of this disease Wesselhoeft and Walcott¹ recently, in an excellent review, have reemphasized the rôle which epidemic parotitis can play in interfering seriously with the training and movements of troops and have clearly defined the *lacunae* in our knowledge and our technic which have rendered prevention and control unsatisfactory

Of these deficiencies perhaps that most keenly felt is the lack of a simple method analogous to the Schick test for determining susceptibility or resistance to infection since on epidemiologic grounds it is highly probable that many individuals who have never experienced an overt attack are nevertheless immune Were such a method available, it is obvious that during an outbreak a considerable number of contacts who, under present conditions, may be subjected to quarantine for several weeks could be safely disregarded Moreover, in dealing with epidemics it would be possible by this means to check the statement of an individual giving a positive history, as it is well known that the history of mumps may often be unreliable

Directly related to the problem of establishing a test for susceptibility are the obviously practical questions of the assay of the prophylactic properties of convalescent or normal human serum and of any vaccine which in the future may be devised For it is evident that if, in a group subjected to study, a significant number of persons are naturally immune who never had recognized mumps, the evaluation of specific prophylactics would be rendered extremely difficult and prolonged in the absence of a means whereby such individuals could be distinguished

With these considerations in mind, we first undertook the study of one of the reactions of immunity in the rhesus monkey—an animal which Johnson and Goodpasture² in 1934 had shown to be susceptible to the virus The information thus obtained was applied to an analysis of the course of events in the disease in human beings and then to the investigation of the immunologic status of normal individuals

* Presented before the New England Regional Meeting of the American College of Physicians, Boston, February 5, 1943

From the Department of Bacteriology and Immunology, Harvard Medical School and School of Public Health, Boston, Mass

A part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College

The data supporting the statements made in this paper will be recorded in detail in subsequent communications A preliminary report on the development of complement-fixing antibodies in infected monkeys and in human beings with mumps has been published (*Proc Soc. Exper Biol and Med*, 1942, 1, 180-184)

We employed the method of inoculation of Johnson and Goodpasture and noted a disease resembling mumps in all important aspects following the instillation of saliva from cases of epidemic parotitis into the salivary ducts of monkeys. In these animals nine serial passages of the virus have been maintained without apparent alteration in its properties by the inoculation of an emulsion of the infected parotid gland removed surgically during the acute phase of the disease. From the operation, recovery is nearly always uneventful.

Since monkeys convalescent from mumps are refractory to reinoculation of the virus, we naturally sought a way of determining whether this immunity might be correlated with the appearance of antibody in the blood serum. For this purpose, the complement fixation test was used in which the antigen consisted of a dilute suspension in saline of the infected parotid gland. As a control a suspension of gland from a normal monkey was regularly included. By this procedure sera of monkeys before inoculation, at the height of the disease, during convalescence and at varying periods thereafter were tested for the presence of antibody. None was detected in the specimens from normal animals or in those taken during the early acute stage. Within three days following the acute stage, however, some antibody was demonstrated and after five days the titer was shown to be high. For a month or somewhat longer this high level was maintained. Gradually the concentration of antibody decreased until amounts comparable to those found in certain normal human beings were reached. The titer then appeared to remain constant for at least 10 months. This persistence of antibody at a low level following recovery is important in relation to the significance of the results obtained in man.

From these data we may conclude, then, that infection of the rhesus monkey with the virus of mumps leads in a short time to the appearance of specific complement fixing antibodies which are not present in normal susceptible animals. Moreover these antibodies may persist in the blood for many months.

By the same procedure sera obtained from mumps patients at comparable periods of the disease have been investigated. Results analogous to those noted in the experiments with animals have been recorded. No antibody was demonstrated in the sera of 10 of 11 cases of typical mumps taken on the first or second day of the disease. It is possible that the patient representing the single exception was ill prior to the recorded time of onset. In five patients when the specimens were first secured on the third to the sixth day of illness, antibody in relatively low titer was found. In these cases, however, as well as in those in which no antibody was initially present, a pronounced increase in antibody concentration has always been subsequently observed. In only one patient have we information concerning a drop in titer from the high level of early convalescence during the following months. But here, at least, the course of events was similar to that in the monkey, since the con-

valescent titer fell within seven months to a level comparable to that found in many normal individuals

A few tests on sera obtained during and after other infections such as influenza-like disease, German measles and scarlet fever have failed to reveal emergence or increase in antibody reacting with the virus of mumps

Thus it would appear that in man as in the monkey specific complement fixing antibody is usually absent in the earliest stage of the clinical disease, appears shortly thereafter, increases markedly in amount, and then decreases to persist for at least some months following recovery

These observations have led to the application of the test as an aid in the diagnosis of cases of encephalitis without definite parotitis, suspected, on clinical grounds, of being attributable to infection with the virus of mumps. In two of six such cases a significant rise in titer has been recorded, and in one of these two no antibody was demonstrated in the specimen taken three days after the onset. It is possible that our failure to demonstrate a rise in titer in every instance may be explained by assuming that encephalitis is a relatively late complication of the infection

In the six encephalitic patients whom we have studied, however, and in whom the clinician suspected mumps virus as the etiologic agent, titers were obtained which were higher than all but one of the normal human sera we have evaluated. Thus we may suggest that in cases of suspected mumps encephalitis without parotitis the complement fixation test should be helpful in confirming the diagnosis

In the light of all the foregoing findings, it became of great interest to ascertain whether the complement fixing antibody was present or absent in the sera of normal individuals of varying ages, since its presence might tentatively be taken to denote previous infection with the virus whether or not this had led to clinically apparent disease. Conversely its absence might be assumed to indicate susceptibility

We have thus far tested the sera of about 265 adults and 115 children. Since in each category many of the histories were unreliable, I will here present only the results of studies carried out on a group of 163 individuals at the Harvard Medical School comprised mostly of male students but including older people as well, together with a small group of 31 normal children three to five years of age attending two day nurseries directed by officials of the Health Department of Boston

The survey on the personnel at the Medical School revealed the following facts. Antibody occurred in about 92 per cent of the sera of those giving a positive history of mumps. In sharp contrast, 50 per cent of the sera of those who denied having had the disease contained antibody

It is possible, then, to assume with some confidence that nearly half those individuals who gave reliable denials of having had mumps, at some time underwent an inapparent or "silent" infection which, in view of the solid and persistent immunity usually conferred by the disease, should render them in-

susceptible On the other hand, the assumption seems justifiable that most of those in whose sera antibody could not be demonstrated did not experience an infection and are therefore potentially susceptible

The experiments with the children yielded additional data of the same sort As one would expect in this age group, the percentage of negative reactors with negative histories was greater

From the standpoint of routine testing of sera, the complement fixation test is laborious and time-consuming With the possibility in mind of the need for studying large groups of individuals, we sought for another reaction of immunity which might be more simply elicited

It had been noted that the antigen used in the complement fixation test was still able to fix complement after heating for 20 minutes at 65° C Under these conditions, however, the infective properties of the virus would presumably be destroyed Because of the fact that heated mumps virus still was capable of reacting with antibody, and because it has been shown that when inactivated by heat the viruses of vaccinia and lymphogranuloma venereum will still elicit skin reactions in those who have previously been infected with active virus, we carried out a series of experiments in which the diluted heat inactivated suspension of infected monkey parotid was injected intradermally in certain of the normal individuals studied for complement fixing antibody Included as control was a heated suspension of normal monkey parotid

At the site of the injection of the infected parotid suspension, in nearly 100 per cent of those giving a history of mumps, an erythematous reaction occurred after 24 to 48 hours, varying from 1 to 4 cm in diameter and often slightly indurated Only a negligible number of reactions occurred at the site of injection of the normal gland material The reactions usually disappeared within one to four days following the fastigium As with the tests for antibody, the group giving no history of mumps revealed about equal numbers of negative and positive reactors Indeed there was evident a close parallelism between the two tests The skin test, however, was positive in those few cases in which a history of mumps was given and the complement fixation test was negative, a fact which suggests that the skin test may be a more delicate indicator of past infection In only one child with negative history, the reverse was observed a negative skin test with positive complement fixation But it should be stated that in a group of abnormal children in a home for the feeble-minded, a higher percentage of reversals of this sort were observed

Although the number of individuals in whom both tests have been applied simultaneously is small, we believe that the results so far obtained strongly imply that a positive skin reaction indicates a previous infection with the virus whereas failure to react signifies in most instances potential susceptibility

As an additional bit of evidence in respect to the specificity of the skin reaction, it can be said that in two patients it has been shown that the skin

test was negative during the acute phase and became positive during convalescence

Finally, it is clear that the exact significance of these findings can only be determined by extensive trials in the field or a critical experiment involving the inoculation of human beings with potent virus

BIBLIOGRAPHY

- 1 WFSSELHOEFT, C, and WAI COTT, C F Mumps as a military disease and its control, War Med, 1942, 11, 213
- 2 JOHNSON, C D, and GOODPASTURE, E W An investigation of the etiology of mumps, Jr Exper Med, 1934, 114, 1

EDITORIAL

*THE COLLEGE AND THE WAR **

The broad educational program of the American College of Physicians was becoming firmly established as the war clouds began to gather. Rooted in the rich soil of medical science with a national faculty unsurpassed for its quality of teaching and research, the annual sessions of the College, the post-graduate courses, the regional meetings and the research fellowships were rapidly extending the influence of the College. These activities were directed to a growing body of physicians diligently bent on improving their knowledge and experience by following close on the heels of a band of brilliant teachers.

Wise leadership in the College, seeing turbulent times ahead, moved for the appointment of a Preparedness Committee before war was declared. In addition, a substantial grant was made to the Committee on Medicine of the National Research Council before funds were available from other sources for the classification and evaluation of physicians. A further grant was made to the National Research Council for the support of research and study of blood plasma at a time when funds were otherwise not forthcoming.

Medicine has a rôle of commanding importance in time of war, in fact, morale and the health of the nation are entrusted to the doctors. When the country was challenged and its security threatened, the College membership offered its services, as a body almost to the man, some to the Army, others to the Navy and still others to the Public Health Service. The latest statistics show the number on active service to be 1427 or 28.4 per cent of the entire College membership. Members of the College in a great many instances occupy responsible positions in the Medical Corps of the Services, from the Surgeons General down. Consultants in Medicine for the Pacific and European areas and the great majority of Consultants in Medicine and Allied Specialties in the eight Service Commands are Fellows of the College.

No figures suggest the large group of teachers, investigators, clinicians and others who were placed on the essential list in the country's great schools of medicine. Many of this group are now blazing new trails on assignments of far-reaching importance, serving on boards of investigation and study under the direction of the National Research Council.

Still another group from the College is contributing in a substantial manner to the war effort by serving on induction boards and in places of civilian service, many of whom were ambitious to don the uniform but, because of age limitation or some slight physical deviation, were victims of the services' rigid regulations. They also serve who stay at home!

* The opinions and assertions contained here in are those of the author and are not to be construed as those of the Navy or of the naval service at large.

Although the annual session of the College for 1943 was cancelled, three postgraduate courses were offered, all of which were oversubscribed. The Surgeons General have encouraged available doctors to attend these courses. Civilian members have found them a beneficial respite from the wearing routine of long hours. Offering a change of atmosphere and an opportunity for an interesting review of medical advances, the postgraduate courses offered by the College may, presumably, find a higher utility in time of war, at least more so than was first thought likely.

Regional meetings in Philadelphia, Chicago, Boston, New Orleans, Washington, Great Falls, Buffalo, Kansas City, Columbus and Jacksonville, with scientific papers of the first importance, have served to stimulate interest where members of the College in the various localities mingle with members of the Services for the purpose of exchanging ideas. In considerable part the topics included in these programs have been selected because they have a distinct bearing on the war effort and present concisely the latest available knowledge on the subjects. The ANNALS OF INTERNAL MEDICINE has devoted this number exclusively to the publication of some of these papers in the belief that they will be of practical value to our younger medical officers as well as interesting to our readers generally.

Medical information created by the concentration and training of troops as well as the newer problems of medical importance arising from an accelerated industrial program is being analyzed. To these are brought the problems of civilian medicine which have gained a new importance because of the war. Preventive medicine, prophylaxis, community and individual vitality, problems of epidemiology, venereology, food supply, fatigue in industry and the services are but a few of the problems being energetically studied by members of the American College of Physicians.

The College has joined with the American Medical Association and the American College of Surgeons in the creation of a plan for mobilizing the most talented teaching personnel of the entire nation in the direction of the Army and Navy hospitals. Under the title of War-Time Graduate Medical Meetings, a committee of three doctors, one from each of the organizations sponsoring the plan, has been appointed. Funds have been appropriated to carry on the work and the program is now well under way.

A teaching faculty has been made available by the combined efforts of the three organizations whereby qualified teachers, selected by National Consultants in some 30 special fields of medicine, are now available for short intensive courses of postgraduate instruction wherever commanding officers of service hospitals desire to avail themselves of such authoritative teaching for the benefit of their respective staffs.

For the purpose of carrying on this nationwide program, the country has been divided into 24 regions and in each region a committee of three serves as a working unit for the implementation of the program. It is noteworthy that it has the authorization of the three Surgeons General.

In our nation where medical science has reached its highest pinnacle, with its great medical faculties and research institutions, leaders are being developed to carry on the work of medical reconstruction, rehabilitation and the wise distribution of medical and nutritional supplies in the war torn nations. This presupposes an international interest and point of view. Science and culture, the dual basis of medicine, know no political boundaries. Medicine needs to hold high the torch of civilization and those qualities of human existence and social welfare that make life worth living, the qualities which the world needs most at the present time. These represent the major fields of interest of the members of the American College of Physicians which explains the high percentage of the membership of the College now in positions of responsibility and importance.

Officials of the College are actively planning for the postwar period. In addition to the immediate needs of doctors for further postgraduate instruction, the encouragement of important researches and the routine life of the College must be carried on. Likewise, the College membership will be called upon to do its part in meeting the extensive needs of the devastated nations. Vision and sound planning today favor prompt action in the field of medical relief tomorrow. American Medicine is facing its greatest opportunity.

EDWARD L. BORTZ,
Commander MC-V(S) USNR

>

REVIEWS

Synopsis of Ano-Rectal Diseases By LOUIS J HIRSCHMAN 315 pages, 13 X 20 cm
C V Mosby Company, St Louis 1942 Price, \$4.50

This little handbook of ano-rectal diseases has been written with great care by one of wide experience in this particular field. The book is small and concise, but covers the subject thoroughly. It contains 194 fine illustrations, twelve of which are in color. In the back of the book there is a symptom index which is helpful.

The book contains a chapter on anatomy which is practical because it has been written especially for those interested in the diagnoses and treatment of ano-rectal conditions. Much space has been devoted to routine diagnostic methods used, and to routine methods of treatment. An appropriate amount of space has been devoted to methods and type of anesthesia. The chapter on focal infection of ano-rectal origin is new and enlightening.

Historical reference, bibliography, and many minute technical details have necessarily been omitted. Also the treatment of major affections of the rectum and colon, which is beyond the scope of this book, has been omitted.

It is obvious that the author has kept in mind the needs of the medical student and the general practitioner while writing this book, and because of this it is valuable, especially from a practical standpoint.

J C D

Infant Nutrition By WILLIAMS McKIM MARRIOTT, B.S., M.D. Revised by P C JEANS, A.B., M.D. 475 pages, 15.5 X 23.5 cm C V Mosby Co., St Louis 1941 Price, \$5.50

The revised edition of this publication keeps it foremost among textbooks dealing with this subject.

There have been added chapters that reflect the newer pediatric thought. Growth and development have been presented in a concise manner quite suitable for the student and the practitioner. The recent advances in the various concepts of metabolic processes and vitamins have been included. The famed acid milk chapter has been improved. The various commercial preparations are nicely evaluated.

The reviewer recommends the book for the student and practitioner because of the sound information that it presents in an easily assimilable form.

J E B

Essentials of Gynecology By WILLARD R COOKE, M.D., F.A.C.S. 474 pages, 16 X 23.5 cm J B Lippincott Company, Philadelphia 1943 Price, \$6.50

This book, dealing with the essentials of gynecology, has grown out of the author's teachings and experience. The author has selected only the genuinely fundamental topics, and by that means has kept the book down to a usable size for the student and practitioner. In the chapters dealing with anatomy, embryology, abnormalities, and functional disturbances emphasis has been placed on elements of practical importance.

Throughout the book the author has included many of his own observations and his own methods of examination, and these are a valuable inclusion. Throughout the book one of the dominant considerations has been the patient as a complete personality. The important aspect of the patient's mode of life and psychology is included, and this adds something too often overlooked.

The book is 475 pages long and contains 197 illustrations, ten of which are in color. Many of the author's original line drawings are included. Most of the illustrations, particularly those of gross specimens and microphotographs, have been taken from the author's own material.

The salient features of anatomy, pathology, symptomatology, and therapy of gynecology have been well presented, and medical treatment has been stressed throughout the book. The chapter on operative gynecology is more or less an outline and is not intended for the practicing gynecologist, but is merely a guide for the student and practitioner. It includes preoperative and postoperative care and a brief outline of the more common gynecological operations.

This book is well written and is a definite expression of the author's ideas, practices, and teachings. It will serve well as a basic course for students.

J C D

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. Second Edition. By JOHN R. PAUL, M.D., and OTHER CONTRIBUTORS. 163 pages, 23.5 × 16 cm. 1943. Published by the Metropolitan Life Insurance Company for the American Heart Association.

Mind, Medicine and Man. By GREGORY ZILBOORG, M.D. With a foreword by ARTHUR H. RUGGLES, M.D. 344 pages, 22 × 15 cm. 1943. Harcourt, Brace and Company, New York, N.Y. Price, \$3.50.

A Text-Book of Pathology. Fourth Edition. Thoroughly Revised. By WILLIAM BOYD (M.D., LL.D., M.R.C.P., Ed., F.R.C.P., Lond., Dipl., Psych., F.R.S.C.). 1008 pages; 24 × 15.5 cm. 1943. Lea and Febiger, Philadelphia. Price, \$10.00.

Methods for Diagnostic Bacteriology. Second Edition. By ISABELLE G. SCHAUB, A.B., and M. KATHLEEN FOLEY, A.B. 430 pages, 22 × 14.5 cm. 1943. C.V. Mosby Company, St. Louis, Missouri. Price, \$3.50.

Neurology. Third Edition. By ROY R. GRINKER, M.D. 1136 pages, 25.5 × 17 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, \$6.50.

La Urobilina en el Estado Normal y Patológico. Segunda Edición. By MARCELO ROYER. 265 pages, 23 × 16 cm. 1943. El Ateneo, Buenos Aires, Argentina.

Primer of Allergy. Second Edition. By WARREN T. VAUGHAN, M.D. 176 pages, 20 × 13 cm. 1943. C.V. Mosby, St. Louis, Missouri. Price, \$1.75.

A Manual of Otolaryngology and Laryngology. Second Edition. By HOWARD CHALKER BATTINGE, M.D., F.A.C.S. 331 pages; 24 × 15 cm. 1943. Lea and Febiger, Philadelphia. Price, \$4.00.

Clinical Significance of the Blood in Tuberculosis. By GUST LINDH MOLLER, M.D. 516 pages, 24 × 16 cm. 1943. The Commonwealth Fund, New York, N.Y. Price, \$3.50.

Hope Deferred. By DANIEL SIEGEL. 536 pages, 22 × 15 cm. 1943. The Macmillan Co., New York, N.Y. Price, \$2.75.

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,411 Fellows and Associates of the College on active military duty. Herewith are reported the names of 19 additional members, bringing the grand total to 1,430.

George O. Bell
Philip G. C. Bishop
Franklin G. Ebaugh
Eugene Eisner
George N. Furbeck
Lewis P. Gundry
Adolph M. Hutter
John S. Kapernick
Richard J. Killhullen
Robert C. Levy

Frank X. Marino
Currier McEwen
Joseph Mignone
Frank T. Moore
Benjamin H. Neuman
Samuel Nesbitt
H. Milton Rogers
James M. Strang
Donald M. Willson

Dr. George A. Cann, F.A.C.P., has been retired from active duty in the Medical Corps of the U. S. Naval Reserve because of physical disability and has returned to private practice in Reno, Nev.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College.

Dr. Archibald Lawrence Hoyne, Chicago, Ill.
Dr. Edgar Paul McNamee, Cleveland, Ohio

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

- Franklin G. Ebaugh, F.A.C.P., Colonel, (MC), U. S. Army—"Psychiatry in Medical Education",
Dr. Oswald F. Hedley, F.A.C.P., U. S. Public Health Service, Bethesda, Md—"Manual of Industrial Hygiene",
Dr. David O. N. Lindberg, F.A.C.P., Oakdale, Iowa—"A Manual of Pulmonary Tuberculosis and an Atlas of Thoracic Roentgenology",
Dr. Francis P. McNamara, F.A.C.P., Dubuque, Iowa—"Collected Reprints of the Medical Staff of Finley Hospital",
Dr. LeRoy Sante, F.A.C.P., St. Louis, Mo—"Manual of Roentgenological Technique, 1943" and "Principles of Roentgenological Interpretation, 1942",
Dr. Alexander S. Wiener (Associate), Brooklyn, N. Y—"Blood Groups and Transfusion"

Reprints

Dr Leon L Blum (Associate), Terre Haute, Ind—1 reprint,
 Joseph G Bohorfoush, F A C P, Major, (MRC), U S Army—1 reprint,
 Dr Verne S Caviness F A C P, Raleigh, N C—4 reprints,
 Dr Donald R Chisholm (Associate) Kealia, Kauai, T H—4 reprints,
 Irving Ershler (Associate), Captain, (MRC), U S Army—3 reprints,
 Dr O P J Falk, F A C P, St Louis Mo—1 reprint,
 Dr Robert H Flinn (Associate), U S Public Health Service, Chicago, Ill—2 reprints,
 John Langdon Gompertz (Associate), Captain, (MRC), U S Army—1 reprint,
 Dr William E Jahsman, F A C P, Ferndale, Mich—2 reprints,
 Dr Abraham M Litvak, F A C P Brooklyn, N Y—2 reprints,
 Samuel Millman, F A C P, Major, (MRC), U S Army—2 reprints,
 Dr William H Ordway, F A C P, Mount McGregor, N Y—1 reprint,
 Dr Hyman I Spector, F A C P, St Louis Mo—7 reprints,
 Dr Alexander S Wiener (Associate), Brooklyn, N Y—7 reprints

Dr Edward A Strecker, F A C P, Philadelphia, Pa, has been named a Consultant in Psychiatry to the Bureau of Medicine and Surgery of the U S Navy

Dr Henry A Luce, F A C P, Detroit, Mich, was recently installed as President of the Michigan Society of Neurology and Psychiatry

Dr. Carl J Wiggers, F A C P, Cleveland, Ohio, spoke on "Recent Studies of the Irreversibility Characteristic of Shock" at a meeting of the Detroit Physiological Society, March 18 On March 26 Dr Wiggers addressed a meeting of the Michigan Academy of Science, Ann Arbor, Mich, on "Recent Observations on the Value of Adrenal Cortex Preparations in Hemorrhagic Shock" and on April 13 presented the Adam Miller Lecture at the Long Island College of Medicine, Brooklyn, N Y, on "Recent Experimental Approaches to the Shock Problem"

The 3rd Annual Meeting of the American Diabetes Association, 1943, has been cancelled

Dr Joseph T Beardswood, Jr, F A C P, Philadelphia, Pa, is the President, Dr Joseph H Barach, F A C P, Pittsburgh, Pa, is 1st Vice President, Dr Russell M Wilder, F A C P, Rochester, Minn, 2nd Vice President, and Dr Cecil Striker, F A C P, Cincinnati Ohio, Secretary Dr Elliott P Joslin, F A C P, of Boston, Mass, is the Honorary President

John Dibble F A C P, Colonel, (MC), U S Army has been reported missing in an airplane accident in the southern Pacific area according to an announcement made in April of this year

Dr. Walter F. Vest F A C P Huntington, W Va, has been appointed Acting Governor for West Virginia to succeed Dr. Albert H Hoge F A C P, Bluefield, who died on April 9, 1943

Among the speakers at a Clinical Research Meeting arranged by the Committee on Medical Education of the New York Academy of Medicine were the following members of the College

- Dr Arthur W. Grace, F A C P, New York, N Y, "The Complement-Fixation Test for Lymphogranuloma Venereum, Results Obtained with Its Use",
 - Dr Thomas H. McGavack, F A C P, New York, N Y, "Neurohormonal Regulation of Water Balance Studies in Patients with Diabetes Insipidus",
 - Dr Randolph West, F A C P, New York, N Y, "Nitrogen Retention, Creatinuria and Other Effects of the Treatment of Simmonds' Disease with Methyl Testosterone",
 - Dr Linn J. Boyd, F A C P, New York, N Y, "The Effect of Sodium Thiosulphate on the Blood",
 - Dr Leo Loewe (Associate), Brooklyn, N Y, "A New Practical Method for the Subcutaneous Administration of Heparin"
-

James S. Simmons, I A C P, Brigadier General, (MC) U S Army, Director of the Preventive Medicine Division, Office of the Surgeon General delivered the John Wickoff Lectures at New York University on April 15 and 16, 1943. General Simmons spoke on "The Preventive Medicine Program of the United States Army", "The Present State of the Army's Health"

General Simmons was recently appointed Lecturer in Public Health at Yale University School of Medicine

Among the speakers at the 52nd Annual Meeting of the Arizona State Medical Association held in Tucson April 30-May 1, were Dr Charles S. Kibler, F A C P, Tucson who spoke on "Demonstration of Heart Disease" and Dr Earle W. Phillips, F A C P, Phoenix "Relief of Allergic Premenstrual Headache"

Dr George Blumer, F A C P, New Haven, Conn., presented the annual George Dock Lecture of the Barlow Society for the History of Medicine at a meeting of the Los Angeles County Medical Association in Los Angeles, Calif., April 2. Dr Blumer spoke on "Remarks on the Life and Accomplishments of William Heberden the Younger"

The California Medical Society held its 72nd Annual Session in Los Angeles, May 2-3. Among the speakers were

- Dr John H. Fitzgibbon, F A C P, Portland, Ore., "Wartime Community Health Problems in Oregon",
 - Dr Tom D. Spies, F A C P, Birmingham, Ala., "Detailed Methods of Diagnosis and Therapy in Acute Nutritive Failure"
-

Dr Edward A. Strecker, F A C P, Philadelphia, Pa., spoke on "Something on Therapy in Alcoholic Conditions" and Dr Harold G. Wolff, F A C P, New York, N Y, spoke on "Emotions and Disease" at a recent series of lectures sponsored by the Graduate Club of the Neuro-Psychiatric Institute of the Hartford Retreat, Hartford, Conn.

The Graduate School of the University of Florida has established a new Department of Medicine, which will be located in Jacksonville and maintained in cooperation with the Medical Society of the State of Florida and the State Board of Health. Dr. Turner Z. Cason, F A C P, College Governor for Florida, Jacksonville, has been named Director of the Department. The new unit will conduct graduate courses and promote research in medicine and surgery. Continuation courses with facilities for clinical instruction for practicing physicians will also be given periodically.

The California Heart Association held its annual meeting in Los Angeles, May 1. Among the speakers were

Dr. Samuel J. McClendon, F A C P, San Diego, "The Incidence of Acute Rheumatic Fever in Southwestern United States",
Richard F. McLaughlin, F A C P, Lieutenant Commander, (MC), U S Naval Reserve, "Rheumatic Infection in a Plateau Area"

Guest speakers at this meeting of the Association were Dr. George Blumer, F A C P, New Haven, Conn., and Dr. Alvin G. Foord, F A C P, Pasadena.

The 151st Annual Meeting of the Connecticut State Medical Society was held in New Haven under the Presidency of Dr. Roy L. Leak, F A C P, Middletown. Among the Fellows of the College who participated were

Dr. George H. Gehrmann, F A C P, Wilmington, Del., "Medicine in Wartime Industry",
Dr. James E. Paullin, F A C P, Atlanta, Ga., President of the College, "The Contribution of the Medical Profession in the Present War Effort",
Dr. John D. Currence, F A C P, New York, N Y, "Arthritic and Rheumatic Conditions Amenable to Physical Therapy",
Dr. Willard C. Rappleye, F A C P, New York, N Y, "Medical Education in Wartime",
Bartholomew W. Hogan, F A C P, Commander, (MC), U S Navy, "Navy Medical Corps in Wartime"

Among the guest speakers at the annual meeting of the Medical Society of the State of New York held in Buffalo, May 3-6, were

Dr. George Baehr, F A C P, Chief Medical Officer, Office of Civilian Defense, Washington, D C, "British and American Experiences in Civil Defense",
Thomas T. Mackie, F A C P, Lieutenant Colonel, (MRC), U S Army, "Tropical Diseases—A Postwar Health Problem"

The New York Heart Association recently formed a Committee on Cardiovascular Diseases in Industry, to aid industry in determining employability of persons with cardiovascular diseases. Dr. Clarence E. de la Chapelle, F A C P, is Chairman of this Committee and Dr. Oswald F. Hedley, F A C P, U. S. Public Health Service, Bethesda, Md., is one of its members.

Dr Albert E Russell, F A C P, U S Public Health Service, Governors Island, N Y, spoke on "Silicosis" at the 90th Annual Session of the Minnesota State Medical Association held in Minneapolis May 17-19

Dr Charles C Bass, F A C P, New Orleans, La, delivered the Ewing Fox Howard Oration at a public session conducted by the Mississippi State Medical Association during their 76th Annual Session in Jackson, May 12-13 Dr Bass spoke on 'Prevention of the Loss of Teeth'

Dr Roger I Lee, F A C P, Boston, Mass, spoke on "Geriatrics The Medical Care of the Elderly" at the 152nd Annual Meeting of the New Hampshire Medical Society in Manchester, May 11

The New York Academy of Medicine has organized a Committee to Study Medicine and the Changing Order The objectives of this Committee are "to be informed on the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future, to define in particular how these changes are likely to affect medicine in its various aspects, to determine how the best elements in the science of medicine and its services to the public may be preserved and embodied in whatever changed social order may ultimately develop" Dr James Alexander Miller, M A C P, Dr Arthur F Chace, F A C P, Dr I Ogden Woodruff, F A C P, all of New York, N Y, Dr Jean A Curran, F A C P Brooklyn, and Dr George Baehr, F A C P, Washington, D C, have been named members of this Committee

Philip W Brown, F A C P, Major, (MRC), U S Army, spoke on "Amebiasis" and Dr W Reece Berryhill, F A C P Chapel Hill, N C, spoke on "Atypical Pneumonia of Unknown Etiology" at the 90th Annual Session of the Medical Society of the State of North Carolina held in Raleigh, May 10-12

Dr Harold M Coon F A C P, Madison, Wis, was recently elected President of the Wisconsin Hospital Association

Dr Samuel B Hadden, F A C P, Philadelphia, Pa spoke on 'Group Psychotherapy' at the annual meeting of the American Neurological Association in New York, N Y May 6-7

The Illinois State Medical Society held its 103rd Annual Meeting in Chicago, May 18-20 Among the guest speakers were Dr Paul A O'Leary, F A C P, Rochester, Minn, who spoke on "Wartime Considerations of Syphilis" and Dr James E Paulin, F A C P, President of the College, Atlanta, Ga, who delivered the annual Oration in Medicine

Dr John R Vonachen, F A C P, Peoria, Ill, participated in a symposium on "Nutrition" and Dr Francis D Murphy, F A C P, Milwaukee, Wis, and Dr Edgar

M Stevenson, F A C P, Bloomington, Ill, conducted a round table discussion on "Cardiovascular Diseases"

The Massachusetts Medical Society held its 162nd Annual Meeting in Boston, May 24-26 Among the guest speakers were

- Dr Thomas Parran F A C P, The Surgeon General, U S Public Health Service, "Wartime Responsibilities of the Public Health Service",
James S Simmons, F A C P, Brigadier General, (MC), U S Army, "Global Malaria",
Dr Russell M Wilder, F A C P, Washington, D C, "Medical Nutritional Requirements in the Time of War",
Dr Alvan L Barach, F A C P, New York, N Y, "Oxygen Therapy, as Related to Gas Poisoning in War and in Civilian Disasters"

Dr George W Thorn, F A C P, Boston, delivered the Shattuck Lecture on "Physiological Considerations in the Treatment of Nephritis," May 25

The Merck Institute for Therapeutic Research, Rahway, N J, a nonprofit corporation founded in 1933 to conduct investigations into the causes, nature and mode of prevention and cure of diseases in men and animals, recently commemorated its tenth anniversary Among the speakers at the anniversary ceremonies were Dr William H Sebrell, Jr, F A C P, U S Public Health Service, Bethesda, Md, Dr Francis G Blake, F A C P, New Haven, Conn, and Dr Russell M Wilder, F A C P, Washington, D C

The Journal of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N C, will be published bimonthly by the students of the medical school The first issue of this new journal was dedicated to Dr Coy C Carpenter, F A C P, Dean of the medical school for his assistance in making this journal possible

Dr Waller S Leathers, F A C P, Nashville, Tenn, was recently elected President of the Basic Science Board of Tennessee, and Dr Edward L Turner, F A C P, Nashville, Vice President

Among the speakers at the 76th Annual Meeting of the West Virginia State Medical Association in Charleston, May 16-18, were

- Dr William H Sebrell, Jr, F A C P, U S Public Health Service, Bethesda, Md, "Maintaining Adequate Nutrition in Wartime",
Dr A Wilbur Duryee, F A C P, New York, N Y, "Peripheral Vascular Disease and Industry"

Dr Edward J Van Liere, F A C P, Dean of the West Virginia University School of Medicine, Morgantown, delivered the Oration on Medicine Dr Van Liere spoke on "The Effect of Anoxia on the Body"

Hugh R Butt, F A C P, Lieutenant, (MC), U S Naval Reserve, spoke on "Gastric and Duodenal Ulcers in the Naval Personnel" and Dr Lewis M Hurxthal, F A C P Boston, Mass, on "The Thyrocardiac—A Review of Six Hundred Cases" at the annual meeting of the American Surgical Association in Cincinnati, Ohio, May 13-14

The 8th Annual Postgraduate Institute of the Philadelphia County Medical Society on the "Management of Emergencies" was held in Philadelphia, Pa, May 11-14, 1943 Among the Philadelphia members of the College who participated in the program were

- Dr William P Belk, F A C P, "The Wassermann Test, Blood Sedimentation Test Plasma Balance in Emergencies",
- Dr John Eiman, F A C P, "Coma from the Urologist's Point of View",
- Dr George Morris Piersol, F A C P, "Coma from the Internist's Point of View",
- Dr Charles L Brown, F A C P, "Diagnosis and Treatment of Acute Cerebral Vascular Accidents",
- Dr Harold W Jones, F A C P, "Agranulocytosis and Hemorrhagic Diseases",
- Dr Harrison F Flippin, F A C P, "Treatment of Septicemia",
- Dr George E Pfahler, F A C P, "Roentgen Ray Treatment of Acute Inflammatory Conditions",
- Dr Stanley P Reimann, F A C P, "Blood Counts, Urinalysis Examination, Blood Typing and Pneumococcus Typing in Emergencies",
- Dr John A Kolmer, F A C P, "Treatment of Acute Bacterial Meningitis",
- Dr Henry L Bockus, F A C P, "Acute Diarrheas",
- Dr William D Stroud, F A C P, "Diagnosis and Treatment of Acute Coronary Occlusion",
- Dr Charles C Wolferth, F A C P, "Diagnosis and Treatment of Angina Pectoris",
- Dr Russell S Boles, F A C P, "Prevention and Medical Management of Acute Complications of Ulcer",
- Dr W Edward Chamberlain, F A C P, "The Roentgen Analysis of Fractures",
- Dr Thomas M McMillan, F A C P, "Diagnosis and Treatment of Acute Pulmonary Edema",
- Dr William G Leaman, Jr, F A C P, "Diagnosis and Treatment of Acute Congestive Heart Failure",
- Dr Louis H Clerf, F A C P, "Foreign Bodies in the Bronchial Air Passages"

Dr A Hamilton Stewart, F A C P, Secretary of Health of the Commonwealth of Pennsylvania Harrisburg, and Dr Augustus S Kech, F A C P, President-Elect of the Medical Society of the State of Pennsylvania, Altoona, were among the guest speakers at the opening day luncheon of the Society

The 51st Annual Session of the Oklahoma State Medical Association was held in Oklahoma City, May 11-12, 1943 Among the speakers were

- Udo J Wile, F A C P, Colonel, U S Public Health Service, Ann Arbor, Mich, "The Rapid Treatment Method for Syphilis",
- Dr Coyne H Campbell, F A C P, Oklahoma City, "Demonstration of Minimum Neuropsychiatric Examination for Inductees",
- Dr Charles E Leonard (Associate), Oklahoma City, "Demonstration of Minimum Neuropsychiatric Examination for Inductees",

Dr C W Arrendell, F A C P, Ponca City, "The Child in the Local Health Program",
 William H Gordon, F A C P, Colonel, (MRC), U S Army, "Neutropenias";
 Dr Homer A Ruprecht, F A C P, Tulsa, "Unusual Findings in Coronary Disease",
 Dr J William Finch, F A C P, Hobart, "Androgenic Therapy in the Female",
 Leslie B Marshall (Associate), Captain, (MC), U S Navy, "Naval Medicine",
 Dr Wann Langston, F A C P, Oklahoma City, "Some Observations on Coronary Disease";
 W Lee Hart, F A C P, Colonel, (MC), U S Army, "Activities of the Medical Department in the Eighth Service Command"

The Medical Association of Georgia held its 94th Annual Session in Atlanta, May 11-14, 1943 Guest speakers on the scientific program included

Dr Chauncey C Maher, F A C P, Chicago, Ill, "Complications of Acute Coronary Thrombosis";
 Dr James H Means, F A C P, Boston, Mass, "Practical Points in the Diagnosis and Treatment of Graves' Disease" and "Some Features of Peptic Ulcer"

The Abner Wellborn Calhoun Lecture of the Association was delivered by Ross T McIntire, F A C P, Rear Admiral, (MC), U S Navy, The Surgeon General Admiral McIntire spoke on "Medical Achievements in This Present War"

Dr Salvador Zubiran, F A C P, Mexico City, D F, is the President of the First National Congress of Public Welfare, called by the President of Mexico, to be held in the City of Mexico, August 15-22, 1943 It is the desire of the officers planning this Congress that leaders in the fields of medicine and public welfare throughout the continent shall attend and thus strengthen the ties of friendship and mutual understanding

REGIONAL MEETING ATTENDANCE

The attendance at three recent Regional Meetings of the American College of Physicians is revealed in the statistics that follow Each meeting presented an excellent program, yet varying in content and in the speakers presenting papers It is felt that no single war-time activity of the College has been of such widespread value as these Meetings Ordinarily, at Annual Sessions, there is a participation by approximately 20 to 23 per cent of the College membership The average participation by members at these Regional Meetings has been about 40 to 42 per cent

The attendance record for three recent Meetings follows (Washington, D C, April 24, 1943—Delaware, Maryland, District of Columbia, Virginia, North Carolina and West Virginia, Kansas City, May 8, 1943—Missouri, Kansas, Oklahoma and Nebraska, Columbus, May 14, 1943—Ohio, Kentucky, West Virginia and Western Pennsylvania)

	Members	% of Membership	Guests	TOTAL	Civilian Doctors	Army	Navy	USPHS
Washington	263	45.5	200	463	200	177	75	11
Kansas City	109	42.4	164	273	172	89	7	5
Columbus	113	27.0	107	220	166	48	4	2

The State of Kansas at the Kansas City Meeting led all other States with a member attendance of 68.6 per cent. At the Washington Meeting, Maryland led with a member attendance of 52.5 per cent. At the Columbus Meeting, Kentucky led with a member attendance of 34.8 per cent.

WAR-TIME GRADUATE MEDICAL MEETINGS

A "Statement of Organization" of the War-Time Graduate Medical Meetings appeared in these columns in the May, 1943, issue. That announcement not only outlined the objectives and purposes of the Central Committee, consisting of Comdr. Edward L. Bortz, Chairman, Philadelphia, Pa., Dr. William B. Breed, Secretary-Treasurer, Boston, Mass., and Dr. Alfred Blalock, Baltimore, Md., but explained the method of operation and delineated the duties of the Section Committees and the Board of Consultants. The program is authorized by the Surgeons General of the U. S. Army, the U. S. Navy and the U. S. Public Health Service, and is a joint project of the American Medical Association, the American College of Physicians and the American College of Surgeons. The organization is national in scope and proposes to organize and conduct graduate instruction in the form of ward walks, clinics, demonstrations, lectures, round tables and conferences to large medical installations in the Armed Forces throughout the nation. The Central Committee has already initiated some of the programs and is now prepared to organize programs at any Service Hospital in which there is a reasonably large number of medical officers and from the commanding officer of which a request is filed for such programs.

Herewith published is the personnel of the Board of National Consultants and the personnel of the Regional Committees.

Board of National Consultants

1 ALLERGY	Robert A. Cooke, F.A.C.P. New York, N. Y.
2 ANESTHESIA	John S. Lundy Rochester, Minn.
3 AVIATION MEDICINE	W. Paul Holbrook, F.A.C.P. Lt. Col., (MC), USA Washington, D. C.
4 CARDIOVASCULAR PROBLEMS	William D. Stroud, F.A.C.P. Philadelphia, Pa.
5 CHEMOTHERAPY	Chester S. Keefer, F.A.C.P. Boston, Mass.
6 DERMATOLOGY	Chester N. Frazier, F.A.C.P. Baltimore, Md.
7 DYSENTERIES	Thomas T. Mackie, F.A.C.P. Lt. Col., (MC), USA Washington, D. C.
8 EPIDEMIOLOGY AND LABORATORY MEDICINE	Roy R. Kracke Decatur, Ga.
9 GASTRO-INTESTINAL DISEASES	Walter L. Palmer, F.A.C.P. Chicago, Ill.
10 GENERAL INTERNAL MEDICINE	David P. Barr, F.A.C.P. New York, N. Y.
11 GENERAL SURGERY	Irvin Abell, F.A.C.S. Louisville, Ky.

- | | |
|---------------------------------------|---|
| 12 MALARIA | Henry E Meleney
New York, N Y |
| 13 NEUROLOGY AND NEURO-SURGERY | Tracy J Putnam
New York, N Y |
| 14 NUTRITION | John B Youmans, F A C P
Nashville, Tenn |
| 15 ORTHOPEDIC SURGERY | George E Bennett, F A C S
Baltimore, Md
and
Frank D Dickson, F A C S
Kansas City, Mo |
| 16 PHYSICAL THERAPY | Frank H Krusen, F A C P
Rochester, Minn |
| 17 PLASTIC AND MAXILLO-FACIAL SURGERY | Robert H Ivy, F A C S
Philadelphia, Pa |
| 18 PSYCHIATRY | Arthur H Ruggles
Providence, R I
and
Edward A Strecker, F A C P
Philadelphia, Pa |
| 19 PSYCHOSOMATIC MEDICINE | John Romano
Cincinnati, Ohio |
| 20 RADIOLOGY | Byrl Kirklin, F A C P
Rochester, Minn |
| 21 RESPIRATORY DISEASES | Francis G Blake, F A C P
New Haven, Conn |
| 22 RHEUMATISM AND ARTHRITIS | Ralph Pemberton, F A C P
Philadelphia, Pa |
| 23 SHOCK, BURNS, AND PLASMA | Douglas B Kendrick, Jr
Lt Col, (MC), U S A
Washington, D C
and
Lloyd R Newhouser, F A C P
Comdr, (MC), U S N
Bethesda, Md |
| 24 THORACIC SURGERY | Leo Eloesser, F A C S
San Francisco, Calif |
| 25 TRAUMATIC SURGERY OF THE ABDOMEN | Frederick A Coller, F A C S
Ann Arbor, Mich |
| 26 TUBERCULOSIS | Esmond R Long
Lt Col, (MC), U S A
Washington, D C |
| 27 UROLOGY | Herman L Kretschmer, F A C S
Chicago, Ill |
| 28 VENEREAL DISEASES | .. Raymond A Vonderlehr
U S Public Health Service
Washington, D C |

Regional Committees

(Appointments by (*) American College of Physicians, (†) American College of Surgeons, (‡) American Medical Association)

Region
No

- 1 MAINE, NEW HAMPSHIRE, VERMONT, MASSACHUSETTS
 *Chester S Keefe, F A C P, Boston, *Chmn*
 †Arthur W Allen, F A C S, Boston
 ‡Merrill C Sosman, Boston
- 2 CONNECTICUT, RHODE ISLAND
 †Creighton Barker, New Haven, *Chmn*
 *Alexander M Burgess, F A C P, Providence
 †Samuel C Harvey, F A C S, New Haven
- 3 NEW YORK
 *Oswald R Jones, F A C P, New York, *Chmn*
 †Henry W Cave, F A C S, New York
 ‡Norman Jolliffe, F A C P, New York
- 4 EASTERN PENNSYLVANIA, DELAWARE, NEW JERSEY
 ‡Eugene P Pendergrass, Philadelphia, *Chmn*
 *George C Griffith, F A C P, Philadelphia
 †J Stewart Rodman, F A C S, Philadelphia
- 5 MARYLAND, DISTRICT OF COLUMBIA, VIRGINIA, WEST VIRGINIA
 *James Alexander Lyon, F A C P, Washington, *Chmn*
 †C Reid Edwards, F A C S, Baltimore
 ‡Francis X McGovern, Washington
- 6 NORTH CAROLINA, SOUTH CAROLINA
 ‡Wingate M Johnson, F A C P, Winston-Salem, *Chmn*
 †James C McLeod, F A C S, Florence
 *Paul F Whitaker, F A C P, Kinston
- 7 GEORGIA, FLORIDA
 *Turner Z Cason, F A C P, Jacksonville, *Chmn*
 †Edward Jelks, F A C S, Jacksonville
 ‡James R McCord, F A C S, Atlanta
- 8 WESTERN PENNSYLVANIA, OHIO
 *Charles A Doan, F A C P, Columbus, *Chmn*
 †Fred M Douglass, F A C S, Toledo
 ‡George R Harris, Pittsburgh
- 9 MICHIGAN
 ‡J Milton Robb, F A C S, Detroit, *Chmn*
 †Archibald D McAlpine, F A C S, Detroit
 *Cyrus C Sturgis, F A C P, Ann Arbor
- 10 KENTUCKY, TENNESSEE
 †Elmer L Henderson, F A C S, Louisville, *Chmn*
 *Chauncey W Dowden, F A C P, Louisville
 ‡Harrison H Shoulders, F A C S, Nashville
- 11 ALABAMA, MISSISSIPPI
 †James M Mason, F A C S, Birmingham, *Chmn*
 *William K Purks, F A C P, Vicksburg
 ‡Alfred A Walker, Birmingham

12 LOUISIANA

- ‡John H Musser, F A C P, New Orleans, *Chmn*
- *Edgar Hull, F A C P, New Orleans
- †Urban Maes, F A C S, New Orleans

13 TEXAS

- ‡Albert O Singleton, F A C S, Galveston, *Chmn*
- ‡Alfred I Folsom, Dallas
- *Charles T Stone, F A C P, Galveston

14 INDIANA, ILLINOIS, WISCONSIN

- *LeRoy H Sloan, F A C P, Chicago, *Chmn*
- †Warren H Cole, F A C S, Chicago
- ‡Newell C Gilbert, Chicago

15 MINNESOTA, IOWA

- ‡William A O'Brien, Minneapolis, *Chmn*
- †James M Hayes, F A C S, Minneapolis
- *Edward H Ryneerson, F A C P, Rochester

16 MISSOURI, KANSAS, ARKANSAS, OKLAHOMA

- †Frank D Dickson, F A C S, Kansas City, *Chmn*
- *O P J Falk, F A C P, St Louis
- ‡Henry H Turner, F A C P, Oklahoma City

17 NORTH DAKOTA, SOUTH DAKOTA, NEBRASKA

- †Angus L Cameron, F A C S, Minot, N D, *Chmn*
- ‡Herman Jahr, Omaha
- *Warren Thompson, F A C P, Omaha

18 MONTANA, WYOMING

- *Ernest D Hitchcock, F A C P, Great Falls, *Chmn*
- ‡Louis W Allard, F A C S, Billings
- †Fred F Attix, F A C S, Lewistown, Mont

19 COLORADO, UTAH

- *James J Waring, F A C P, Denver, *Chmn*
- ‡John W Amessee, Denver
- †Casper F Hegner, F A C S, Denver

20 NEW MEXICO, ARIZONA

- ‡Carl Mulky, F A C P, Albuquerque, *Chmn*
- *Fred G Holmes, F A C P, Phoenix
- †Charles B Palmer, F A C S, Phoenix

21 WASHINGTON

- †John H O'Shea, F A C S, Spokane, *Chmn*
- *Edwin G Bannick, F A C P, Seattle
- ‡Herbert E Coe, F A C S, Seattle

22 IDAHO, OREGON

- ‡John H Fitzgibbon, F A C P, Portland, *Chmn*
- *T Homer Coffen, F A C P, Portland
- †Thomas M Joyce, F A C S, Portland

23 NEVADA, NORTHERN CALIFORNIA

- *Ernest H Falconer, F A C P, San Francisco, *Chmn*
- ‡Arthur L Bloomfield, F A C P, San Francisco
- †Henry H Searls, F A C S, San Francisco

24 SOUTHERN CALIFORNIA

- *Roy E Thomas, F A C P, Los Angeles, *Chmn*
- †Verne C Hunt, F A C S, Los Angeles
- ‡Burrell O Raulston, F A C P, Los Angeles

OBITUARIES

DR F B WATKINS

In the recent death of Dr F B Watkins the American College of Physicians has suffered the loss of a distinguished member. A native of Rutherford County, North Carolina, Fonso Butler Watkins was born April 12, 1878, son of Galeb Whicker and Quintina Wallace Watkins. He was graduated from the University of North Carolina in 1900, and was a member of Phi Beta Kappa. After teaching school for a time in the State of Georgia, he entered the Jefferson Medical College, where he graduated in 1907. He then served an internship in Philadelphia, after which he entered practice in Concord, North Carolina. He remained in private practice only six months, when he joined the staff of the State Hospital in Morganton, where he served continuously for thirty-three years. During his stay at the Morganton institution, he served as assistant superintendent until 1938 when he became superintendent of the institution.

Dr Watkins was prominent in professional circles and reflected credit upon all organizations to which he belonged. At the time of his death he was President of the North Carolina Neuro-Psychiatric Society. Being of a retiring nature, Dr Watkins was not intimately known by a large number of people. Those who did know him, however, were rewarded by a worthy, a sincere, and a loyal friendship. He was genuinely respected by his colleagues and his friends throughout the State in which he lived and labored. By his sterling worth he has left a rich heritage to his wife, Mrs Helen Watrous Watkins and his son, William Downing Watkins, who like his father, is preparing himself for a medical career at the University of North Carolina.

In declining health for some time, he bore bravely and with fortitude an investigation of the institution which he headed, an investigation which was brought about through no fault of his own, and which left his sterling character unblemished. Although his sensitive nature must have suffered, like the good soldier that he was, he suffered in silence.

A fitting tribute to Dr Watkins is the following editorial from the Winston-Salem Journal and Sentinel, entitled "Able State Servant."

"The death of Dr F B Watkins, superintendent of the Western Hospital for the Insane, at a Rutherfordton hospital, removes from the service of the State one of its ablest servants.

"It is significant that while the State Hospital at Morganton has been subjected to much publicity of an adverse nature during the past two years, no breath of scandal or charges of incompetence or negligence involved Dr Watkins. His difficulties at Morganton were apparent to all who knew anything about the mental institution which he headed. Like the Israelites who were enslaved by the Pharaohs in Egypt, he was forced to 'make brick without straw.' And in the face of tremendous odds and severe handicaps he did accomplish remarkable results.

"Dr Watkins was genial, humane, sympathetic of manner, a keen student of psychiatry. He knew human nature, normal and abnormal. He resisted the lure of private practice to devote his life to the cause of the most helpless and in many cases the most hopeless wards of the commonwealth, and for many years as assistant to the superintendent, and as superintendent, endeavored to do the work of two or three psychiatrists and physicians, at the same time doing a prodigious amount of executive work.

"No doubt this over-exertion is one reason why Dr Watkins is dead at the age of 64. The State of North Carolina owes much to this selfless minister to minds diseased, and there are many beneficiaries of his ministrations who will today rise up in many sections of the State to call him blessed."

The American College of Physicians was honored to count Dr Watkins among its Fellows, and with his family and friends feels a genuine loss in his passing.

PAUL F. WHITAKER, M.D., F.A.C.P.,
Governor for North Carolina

DR. JOHN WILLIAM STOFER

Dr. John William Stofer, F.A.C.P., a long honored physician of Gallup, New Mexico, died January 16, 1943, at the age of sixty-four of cerebral hemorrhage. Dr. Stofer received his M.D. degree at the University Medical College of Kansas City in 1908 and a year later came to Gallup. He lived and practiced there continuously, with the exception of one year, 1916-17, until about a year before his death when ill health forced his retirement.

Dr. Stofer was for many years on the Staff of St. Mary's Hospital. He had served as President of the McKinley County Medical Society and of the New Mexico Medical Society and had been a Fellow of the American College of Physicians since 1931. He was interested in Masonic affairs and, while taking part in many of the social activities of his professional associations, was more interested in his professional work. His loss is felt as a friend, and as a highly esteemed and faithful physician.

ROBERT O. BROWN, M.D., F.A.C.P.,
Governor for New Mexico

DR. ARCHIBALD S. DENNISON

Dr. Archibald S. Dennison, F.A.C.P., died suddenly January 22, 1943, at his home in Lynn, Massachusetts. Although his health had been failing for months, he kept up his active practice until the day before his death. Born in Bridgetown, Nova Scotia, in 1869 Dr. Dennison went to Lynn in his early youth and spent his entire professional life in that city where he practiced as a well-loved family physician up to the time of his death. His professional standing locally, as well as with the medical fraternity of Greater Boston, was high.

Dr. Dennison's professional education was acquired in the Bellevue Hospital Medical College where he received an M.D. degree in 1896. For many years he was an active and honorary member of the medical staff of the Lynn Hospital. Dr. Dennison was elected to Fellowship in the American College of Physicians in 1921 and was also a member of the New England Pediatric Society, the Massachusetts Medical Society, and a Fellow of the American Medical Association.

Dr. Dennison is survived by a daughter, Barbara, and a son, Frederick C. Dennison, M.D., of Thomaston, Maine, who is now serving in Alabama as Lieutenant in the Army Air Force.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts

Erratum In the article by Dr. David I. Macht on "Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs" in the ANNALS OF INTERNAL MEDICINE, May 1943, page 782, an error was made in the illustration. In preparing the plate, the upper portion of the original photograph was cut away, and with this the tracing of the respirations during the experiment. The figure will be published in correct form in the author's reprints. We regret the error.

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 18, January-June, 1943

- | | | | |
|--|-----|---|------|
| ALT, H L, S M FEINBERG, — and R
H YOUNG Allergy to Injectable
Liver Extracts, Clinical and Immuno-
logical Observations | 311 | BLACKMAN, S S, JR, J A LUETSCHER,
JR and — Severe Injury to Kid-
neys and Brain Following Sulfathiazole Administration High Serum
Sodium and Chloride Levels and Per-
sistent Cerebral Damage | 741 |
| ASHBURN, F S, J A BARGEN, W W
LINDAHL, — and J DEJ PEMBERTON
Ileostomy for Chronic Ulcerative
Colitis (End Results and Complica-
tions in 185 Cases) | 43 | BLUMSTEIN, A and A B BAKER
Arachnoiditis (Diffuse Proliferative
Leptomeningitis) | 809 |
| ATKINSON, M Ménière's Syndrome
and Migraine, Observations on a
Common Causal Relationship | 797 | BOOTS, E C 35 mm Films in Diag-
nosis of Chest Conditions | 997 |
| BAKER, A B, A BLUMSTEIN and —
Arachnoiditis (Diffuse Proliferative
Leptomeningitis) | 809 | BORMAN, M C Calcification of Left
Ventricular Infarction Recognized
during Life <i>Case Rep</i> | 857 |
| BAREFOOT, S W and J L CALLAWAY
Exfoliative Dermatitis Due to Pheno-
barbital <i>Case Rep</i> | 105 | BORTZ, E L The College and the War,
<i>Edit</i> | 1020 |
| BARGEN, J A, W W LINDAHL, F S
ASHBURN and J DEJ PEMBERTON
Ileostomy for Chronic Ulcerative
Colitis (End Results and Complica-
tions in 185 Cases) | 43 | BRAHDY, L and S KAHN Clinical Ap-
proach to Alleged Traumatic Disease | 491 |
| BARTELS, E C Successful Treatment
of Gout | 21 | BRANSFORD, P W, V W LOGAN and —
Peptic Ulcer in the United States
Navy | 929 |
| BAUER, L H Aviation Medicine—A
Brief History The Physical Qualifica-
tions for Flying, Oxygen Want and the
Use of Supplementary Oxygen | 15 | BROSIN, H W, F G EBAUGH and —
Traumatic Psychoses | 666 |
| BENSON, M E, P A VAN PERNIS, —
and P H HOLINGER Laryngeal and
Systemic Histoplasmosis (Darling)
<i>Case Rep</i> | 384 | BUSCH, I, I W HELD and — Cancer
of the Stomach with Special Refer-
ence to Early Diagnosis | 719 |
| BERESFORD, S, S POLSKY and —
Some Probative Aspects of the Early
Germanic Codes, Carolina and Bam-
bergensis | 841 | BYRON, C S and S MICHALOVER
Calcinosis and Scleroderma with
Parathyroidectomy <i>Case Rep</i> | 225 |
| BIRTHILL, F H Leukemia The Rela-
tive Incidence of Its Various Forms,
and Their Response to Radiation
Therapy | 757 | CALLAWAY, J L, S W BAREFOOT and
— Exfoliative Dermatitis Due to
Phenobarbital <i>Case Rep</i> | 105 |
| BIRSMAN, W, W M SIMPSON and —
Fever Therapy <i>Rev</i> | 414 | CHAFEE, Z, JR Privileged Communi-
cations Is Justice Served or Ob-
structed by Closing the Doctor's
Mouth on the Witness Stand? | 606 |
| | | CHAMBERLAIN, F L, M SOKOLOW and
— Clinical Evaluation of Cedilanid | 204 |
| | | CLINTON, M, JR, G W THORN, J T
QUINBY and — A Comparison of
the Metabolic Effects of Isocaloric
Meals of Varying Composition with
Special Reference to the Prevention of
Postprandial Hypoglycemic Symp-
toms | 913 |

- COL, F O, W M YATER and — Ten Years' Experience with Thorotrast Hepatosplenography 350
- CONNOR, C A R, M W JOHANNSEN and — Cor Pulmonale with Bilateral Aneurysms of the Pulmonary Artery, Interventricular Septal Defect, Patent Ductus Arteriosus and Terminal Ayerza's Syndrome *Case Rep* 232
- COOKE, W R Essentials of Gynecology *Rev* 1023
- CORCORAN, A C, I H PAGE, O M HELMER, K G KOHLSTAEDT, G F KEMPF, — and R D TAYLOR A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 29
- COVEY, G W Chronic Cor Pulmonale *Case Rep* 851
- CRAIG, C F Laboratory Diagnosis of Protozoan Diseases *Rev* 704
- DAVIS, N S III Factors Which May Influence Senescence 81
- DESANCTIS, A G, Editor Advances in Pediatrics *Rev* 704
- DODD, E M Contracts Not to Practice Medicine 618
- DOLGER, H, M ELLENBERG, — and H POLLACK Postoperative Precipitation of Vitamin Deficiencies *Case Rep* 110
- DONALDSON, S W Medical Facts That Can or Cannot Be Proved by Roentgen-Ray, Historical Review and Present Possibilities 535
- DUNCAN, R E The Problems of the Internist in the Navy 920
- DURHAM, R H, W E JAHSMAN and — Recognition of Incipient Thromboangitis Obliterans in Young Draftees 164
- EBAUGH, F G A Review of the Drastic Shock Therapies in the Treatment of the Psychoses 279
- EBAUGH, F G and H W BROSIK Traumatic Psychoses 666
- ELLENBERG, M, H DOLGER and H POLLACK Postoperative Precipitation of Vitamin Deficiencies *Case Rep* 110
- ELLIS, F W and J C KRANTZ, JR Sugar Alcohols XXIV The Metabolism of Sorbitol in Diabetes 792
- ENDERS, J F Observations on Immunity in Mumps 1015
- EWALT, J R, E H PARSONS, S L WARREN and S L OSBORNE Fever Therapy Technique *Rev* 255
- FEINBERG, S M, H L ALT and R H YOUNG Allergy to Injectable Liver Extracts, Clinical and Immunological Observations 311
- FETTER, F Carcinoma of the Lung, A Review of 31 Proved Cases at the Philadelphia Naval Hospital 978
- FLEXNER, J, N E ROSSETT and — A Method for the Continuous Recording of Gastric pH in Situ IV Further Evaluation of the Efficacy of Antacids in Vitro and in the Human Being 193
- FRISCH, A W, A E PRICE and G B MYERS Type VIII Pneumococcus Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers 271
- GALBREATH, W R and E HULL Sulfonamide Therapy of Bacterial Endocarditis, Results in 42 Cases 201
- GIBBS, F A The Present Status of Clinical Electroencephalography 1012
- GIBSON, R B, M LADD and — Legal-Medical Aspects of Blood Tests to Determine Intoxication 564
- GOLDBERGER, M A Gynecologic Surgery *Rev* 870
- GOLDBURGH, H L and B A GOULEY Sulfur Dioxide Chemical Pneumonia, Report of a Case with Recovery Following Accidental Explosion of a Refrigerator Unit *Case Rep* 237
- GOULEY, B A, H L GOLDBURGH and — Sulfur Dioxide Chemical Pneumonia, Report of a Case with Recovery Following Accidental Explosion of a Refrigerator Unit *Case Rep* 237
- GRANT, D N W Medical Aspects of High Altitude Flight 1006
- GRANT, D N W Medical Care of Aviation Personnel 926
- GRISWOLD, E N The Doctor's Federal Taxes 647

- HEDLEY, O F The Fraudulent Use of Digitalis to Simulate Heart Disease 154
- HELD, I W and I BUSCH Cancer of the Stomach with Special Reference to Early Diagnosis 719
- HELMER, O M, I H PAGE, — K G KOHLSTAEDT, G F KEMPF, A C CORCORAN and R D TAYLOR A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 29
- HIRSCHMAN, L J Synopsis of Anorectal Diseases *Rev* 1023
- HOLINGER, P H, P A VAN PERNIS, M E BENSON and — Laryngeal and Systemic Histoplasmosis (Darling) *Case Rep* 384
- HOMANS, J Circulatory Deficiency in the Extremities in Relation to Medico-Legal Problems Arteriosclerotic Deficiency (Including Diabetes), Thromboangitis Obliterans, or Buerger's Disease 518
- HUGHES, C L, W A WINN, — and J M SANDERS Subacute Bacterial Endarteritis Complicating Patent Ductus Arteriosus Case Report with Recovery Following Sulfapyridine-Heparin Therapy *Case Rep* 242
- HULL, E, W R GALBREATH and — Sulfonamide Therapy of Bacterial Endocarditis, Results in 42 Cases 201
- HUMPHREYS, E M, W L PALMER, R SCHINDLER, F E TEMPLETON and — Syphilis of the Stomach *Case Rep* 393
- JAHSMAN, W E and R H DURHAM Recognition of Incipient Thromboangitis Obliterans in Young Draftees 164
- JOHANNSEN, M W and C A R CONNOR Cor Pulmonale with Bilateral Aneurysms of the Pulmonary Artery, Interventricular Septal Defect, Patent Ductus Arteriosus and Terminal Auerz's Syndrome *Case Rep* 232
- JOHLIN, J M Introduction to Physical Biochemistry *Rev* 116
- KAHN, S, L BRAHDA and — Clinical Approach to Alleged Traumatic Disease 491
- KEMPF, G F, I H PAGE, O M HELMER, K G KOHLSTAEDT, — A C CORCORAN and R D TAYLOR A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 2
- KIRSNER, J B and W L PALMER Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function *Case Rep* 11
- KLEIN, C, G SALAND and H ZURROW Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease 21
- KLINGHOFFER, K A, M TAGER and — Acute Thrombocytopenic Purpura Hemorrhagica with Lymphocytosis *Case Rep* 5
- KOEHLER, A E and E WINDSOR The Effectiveness of Replacement Therapy in Achlorhydria 18
- KOHLSTAEDT, K G, I H PAGE, O M HELMER, —, G F KEMPF, A C CORCORAN and R D TAYLOR A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 2
- KRANTZ, J C, JR, Editor Formulary and Handbook of The Johns Hopkins Hospital *Rev* 25
- KRANTZ, J C, JR, F W ELLIS and — Sugar Alcohols XXIV The Metabolism of Sorbitol in Diabetes 79
- KUNDERT, P R, M MALLORY, F MATHERS, L M ORR II and — Circulatory Disturbances in Prostatic Hypertrophy 8.
- LADD, M and R B GIBSON Legal-Medical Aspects of Blood Tests to Determine Intoxication 57
- LA DUE, J S Myxedema Heart A Pathological and Therapeutic Study 35
- LANGE, K A Recording Sphygmotonomograph A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man 30.
- LER, W E The Relation of the Crush Syndrome to That of Burns and Other Types of Traumatic Wounds of Human Tissues 991

- LENNON, W G Newer Knowledge of Epilepsy 145
- LINDAHL, W W, J A BARGEN, — F S ASHBURN and J DEJ PEMBERTON Ileostomy for Chronic Ulcerative Colitis (End Results and Complications in 185 Cases) 43
- LOGAN, V W and P W BRANSFORD Peptic Ulcer in the United States Navy 929
- LUETSCHER, J A, JR and S S BLACKMAN, JR Severe Injury to Kidneys and Brain Following Sulfathiazole Administration High Serum Sodium and Chloride Levels and Persistent Cerebral Damage 741
- LION, B B V Tuning Fork Auscultation A Test for Abdominal Adhesions 297
- MACHT, D I Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs 772
- MALLORY, M, F MATHERS, L M ORR II and P R KUNDERT Circulatory Disturbances in Prostatic Hypertrophy 835
- MARRIOTT, W MCK Infant Nutrition *Rev* 1023
- MARTIN, G J, E H RENNEBAUM and M R THOMPSON Prophylactic and Therapeutic Detoxication Guanidine, Indole and Histamine 57
- MATHERS, F, M MALLORY, — L M ORR II and P R KUNDERT Circulatory Disturbances in Prostatic Hypertrophy 835
- MCCLELLAN, W S New Trends in the Treatment of Chronic Disease An Experience in Spa Therapy 825
- MICHALOVER, S, C S BYRON and — Calcinosis and Scleroderma with Parathyroidectomy *Case Rep* 225
- MIDDLETON, W S Abdominal Pain in Pulmonary Thrombosis 345
- MUELLER, J H The Relation of the Carrier to Epidemic Meningitis 974
- MURPHY, F D and W D WOOD Acute Nephritis and the Effect of Sulfonamides on the Kidneys 999
- MYERS, G B, A W FRISCH, A E PRICE and — Type VIII Pneumococcus Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers 271
- MYERSON, A Certain Medical and Legal Phases of Eugenic Sterilization 580
- NEAL, J B Encephalitis, A Clinical Study *Rev* 414
- ORR, L M II, M MALLORY, F MATHERS, — and P R KUNDERT Circulatory Disturbances in Prostatic Hypertrophy 835
- OSBORNE, S L, J R EWALT, E H PARSONS, S L WARREN and — Fever Therapy Technique *Rev* 255
- PAGE, I H, O M HELMER, K G KOHLSTAEDT, G F KEMPF, A C CORCORAN and R D TAYLOR A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 29
- PALMER, W L, J B KIRSNER and — Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function *Case Rep* 100
- PALMER, W L, R SCHINDLER, F E TEMPLETON and E H HUMPHREYS Syphilis of the Stomach *Case Rep* 393
- PARSONS, E H Military Neuropsychiatry in the Present War 935
- PARSONS, E H, J R EWALT, — S L WARREN and S L OSBORNE Fever Therapy Technique *Rev* 255
- PECK, F B Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin 177
- PEMBERTON, J DEJ, J A BARGEN, W W LINDAHL, F S ASHBURN and — Ileostomy for Chronic Ulcerative Colitis (End Results and Complications in 185 Cases) 43
- POLLACK, H, M ELLENBERG, H DOLGER and — Postoperative Precipitation of Vitamin Deficiencies *Case Rep* 110
- POLSKY, S and S BERESFORD Some Probative Aspects of the Early Germanic Codes, Carolina and Bambergenesis 841

- POWELL, T R Compulsory Vaccination and Sterilization Constitutional Aspects 637
- PRICE, A E, A W FRISCH, — and G B MYERS Type VIII Pneumococcus Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers 271
- QUINBY, J T, G W THORN, — and M CLINTON, JR A Comparison of the Metabolic Effects of Isocaloric Meals of Varying Composition with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms 913
- RENNEBAUM, E H, G J MARTIN, — and M R THOMPSON Prophylactic and Therapeutic Detoxication Guanidine, Indole and Histamine 57
- RHOADS, J E Problems of Fluid Balance in the Traumatized Patient 988
- ROBERTSON, O H Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention 1
- ROSSETT, N E and J FLEXNER A Method for the Continuous Recording of Gastric pH in Situ IV Further Evaluation of the Efficacy of Antacids in Vitro and in the Human Being 193
- SALAND, G, C KLEIN, — and H ZURROW Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease 214
- SANDERS, J M, W A WINN, C L HUGHES and — Subacute Bacterial Endarteritis Complicating Patent Ductus Arteriosus Case Report with Recovery Following Sulfapyridine-Heparin Therapy *Case Rep* 242
- SCHINDLER, R, W L PALMER, — F C TEMPLETON and E H HUMPHREYS Syphilis of the Stomach *Case Rep* 393
- SCHWARTZ, L Problems of Proof in Claims for Recovery for Dermatitis 500
- SCOTT, A W Tort Liability of Hospitals 630
- SHAFER, J H Tularemia, A Report of Four Cases with Unusual Contacts 72
- SIMPSON, W. M. and W BIERMAN Fever Therapy *Rev* 411
- SMITH, H W Scientific Proof and Relations of Law and Medicine 450
- SNYDER, LEM. Criminal Interrogation with the Lie Detector, Eight Years' Experience by the Michigan State Police 551
- SOKOLOV, M and F L CHAMBERLAIN Clinical Evaluation of Cediland 204
- SOLOMON, W M Amyloidosis in Chronic Atrophic Arthritis. *Case Rep* 846
- STEARNS, A W Medical and Social Factors in Crime 599
- STIEGLITZ, E J Pertinent Problems of Geriatric Medicine 89
- STRECKER, E A The Leaven of Psychosomatic Medicine 736
- STUBENBORD, W D Paroxysmal Auricular Fibrillation in Association with Hiatus Hernia *Case Rep* 406
- TAGER, M and K A KLINGHOFFER Acute Thrombocytopenic Purpura Hemorrhagica with Lymphocytosis *Case Rep* 96
- TAYLOR, G B. Fever Therapy 968
- TAYLOR, R D, I H PAGE, O M HELMER, K G KOHLSTAEDT, G F KEMPF, A C CORCORAN and — A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts 29
- TEMPLETON, F E, W L PALMER, R SCHINDLER, — and E H HUMPHREYS Syphilis of the Stomach *Case Rep* 393
- THOMPSON, M R, G J MARTIN, E H RENNEBAUM and — Prophylactic and Therapeutic Detoxication Guanidine, Indole and Histamine 57
- THORN, G W, J T QUINBY and M CLINTON, JR A Comparison of the Metabolic Effects of Isocaloric Meals of Varying Composition with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms 913
- VAN LIERE, E J Anoxia, Its Effect on the Body *Rev* 870
- VAN PLEUNIS, P. A, M E BENSON and P H HOINGLER Laryngeal and Systemic Histoplasmosis (Darling) *Case Rep* 384

- | | | | |
|---|-----|--|-----|
| WARREN, S L, J R EWALT, E H
PARSONS, — and S L OSBORNE
Fever Therapy Technique <i>Rev</i> | 255 | YASKIN, J C The Treatment of Func-
tional Gastrointestinal Disturbances
of Neuropsychiatric Origin | 949 |
| WHITE, P D Cardiac Problems in
War Time | 323 | YATER, W M and F O COE Ten
Years' Experience with Thorotrast
Hepatosplenography | 350 |
| WINDSOR, E, A E KOEHLER and —
The Effectiveness of Replacement
Therapy in Achlorhydria | 182 | YOUNG, R H, S M FEINBERG, H L
ALT and — Allergy to Injectable
Liver Extracts, Clinical and Immuno-
logical Observations | 311 |
| WINN, W A, C L HUGHES and J
M SANDERS Subacute Bacterial
Endarteritis Complicating Patent
Ductus Arteriosus Case Report with
Recovery Following Sulfapyridine-
Heparin Therapy <i>Case Rep</i> | 242 | ZIEGLER, L H Psychoneuroses in War
Time | 941 |
| WOOD, W D, F D MURPHY and —
Acute Nephritis and the Effect of
Sulfonamides on the Kidneys | 999 | ZURROW, H, C KLEIN, G SALAND and
— Pancreatic Tissue Extract (In-
sulin-Free) in the Treatment of Pe-
ripheral Vascular Disease | 214 |

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 18, January-June, 1943

- A**DBOMINAL Adhesions, A Test for — Tuning Fork Auscultation — B B V LYON 297
- Abdominal Pain in Pulmonary Thrombosis W S MIDDLETON 345
- Achlorhydria, The Effectiveness of Replacement Therapy in — A E KOEHLER and E WINDSOR 182
- Allergy to Injectable Liver Extracts, Clinical and Immunological Observations S M FEINBERG, H L ALT and R H YOUNG 311
- Amyloidosis in Chronic Atrophic Arthritis W M SOLOMON *Case Rep* 846
- Ano-Rectal Diseases, Synopsis of — L J HIRSCHMAN *Rev* 1023
- Anoxia, Its Effect on the Body E J VAN LIERE *Rev* 870
- Antacids, Further Evaluation of the Efficacy of — in Vitro and in the Human Being A Method for the Continuous Recording of Gastric pH in Situ IV — N E ROSSITT and J FLEXNER 193
- Arachnoiditis (Diffuse Proliferative Lep-
tomeningitis) A BLUMSTEIN and A B BAKER 809
- Auricular Fibrillation, Paroxysmal — in Association with Hiatus Hernia W D STUBENBORD *Case Rep* 406
- Aviation Medicine—A Brief History The Physical Qualifications for Flying, Oxygen Want and the Use of Supplementary Oxygen L H BAUER 15
- Aviation Personnel, Medical Care of — D N W GRANT 926
- B**ACTERIAL Endocarditis, Sulfonamide Therapy of —, Results in 42 Cases W R GAIBREATH and E HULL 201
- Biochemistry, Introduction to Physical — J M JOHLIN *Rev* 116
- Blood Tests to Determine Intoxication, Legal-Medical Aspects of — M LADD and R B GIBSON 561
- Brain, Severe Injury to Kidneys and — Following Sulfathiazole Administration High Serum Sodium and Chloride Levels and Persistent Cerebral Damage J A LUETSCHER, JR and S S BLACKMAN, JR 741
- Burns, The Relation of the Crush Syndrome to That of — and Other Types of Traumatic Wounds of Human Tissues W E LEE 991
- C**ALCIFICATION of Left Ventricular Infarction Recognized during Life M C BORMAN *Case Rep* 857
- Calcinosis and Scleroderma with Parathyroidectomy C S BYRON and S MICHALOVER *Case Rep* 225
- Cancer of the Stomach with Special Reference to Early Diagnosis I W HLLD and I BUSCH 719
- Carcinoma of the Lung, A Review of 31 Proved Cases at the Philadelphia Naval Hospital F FRTTFR 978
- Cardiac Problems in War Time P D WHITE 323
- Cedilanid, Clinical Evaluation of — M SOKOLOV and F L CHAMBERLAIN 204
- Chest Conditions, 35 mm Films in Diagnosis of — E C BOOTS 997
- Circulatory Deficiency in the Extremities in Relation to Medico-Legal Problems Arteriosclerotic Deficiency (Including Diabetes), Thromboangitis Obliterans, or Buerger's Disease J HOMANS 518
- Circulatory Disturbances in Prostatic Hypertrophy M MAILORY, F MATHLRS, L M ORR, II and P R KLUNDRT 835
- Colitis, Ileostomy for Chronic Ulcerative — (End Results and Complications in 185 Cases) J A BARGIN, W W LINDAHL, F S ASHBURN and J DE J PIMBERTON 43
- College and the War, The — E L BOITZ *Ldit* 1020

- Contracts Not to Practice Medicine
E M DODD 618
- Cor Pulmonale, Chronic — with Report
of a Case G W COVER *Case Rep* 851
- Cor Pulmonale with Bilateral Aneu-
rysms of the Pulmonary Artery, In-
terventricular Septal Defect, Patent
Ductus Arteriosus and Terminal
Auerza's Syndrome M W JOHAN-
SEN and C A R CONNOR *Case Rep* 232
- Crime, Medical and Social Factors in
— A W STEARNS 599
- Criminal Interrogation with the Lie
Detector, Eight Years' Experience by
the Michigan State Police LEM
SNYDER 551
- Crush Syndrome, The Relation of the
— to That of Burns and Other Types
of Traumatic Wounds of Human Tis-
sues W E LEE 991
- D**ERMATITIS, Exfoliative — Due
to Phenobarbital S W BARE-
FOOT and J L CALLAWAY *Case Rep* 105
- Dermatitis, Problems of Proof in Claims
for Recovery for — L SCHWARTZ 500
- Detoxication, Prophylactic and Thera-
peutic — Guanidine, Indole and
Histamine G J MARTIN, E H
RENNERBAUM and M R THOMPSON 57
- Diabetes, Hyperglycemia and Glyco-
suria as Means of Controlling Prota-
mine Zinc Insulin Administration in
— *Edit* 112
- Diabetes, The Metabolism of Sorbitol
in — Sugar Alcohols XXIV —
F W ELLIS and J C KRANTZ, JR 792
- Digitalis, The Fraudulent Use of — to
Simulate Heart Disease O F HED-
LEY 154
- Disease, New Trends in the Treatment
of Chronic — An Experience in Spa
Therapy W S McCLELLAN 825
- Ductus Arteriosus, Subacute Bacterial
Endarteritis Complicating Patent —
Case Report with Recovery Following
Sulfapyridine-Heparin Therapy W
A WINN, C L HUGHES and J M
SANDERS *Case Rep* 242
- Encephalitis, A Clinical Study J B
NEAL *Rev* 414
- Endarteritis, Subacute Bacterial —
Complicating Patent Ductus Arteri-
osus Case Report with Recovery
Following Sulfapyridine-Heparin
Therapy W A WINN, C L
HUGHES and J M SANDERS *Case
Rep* 242
- Endocarditis, Sulfonamide Therapy of
Bacterial —, Results in 42 Cases
W R GALBREATH and E HULL 201
- Epidemic Keratoconjunctivitis *Edit* . 866
- Epidemic Meningitis, The Relation of
the Carrier to — J H MUELLER 974
- Epilepsy, Newer Knowledge of — W
G LENNOX 145
- Eugenic Sterilization, Certain Medical
and Legal Phases of — A MYER-
SON 580
- Exfoliative Dermatitis Due to Pheno-
barbital S W BAREFOOT and J L
CALLAWAY *Case Rep* 105
- F**EVER Therapy G B TAYLOR 968
- Fever Therapy W M SIMPSON
and W BIERMAN *Rev* 414
- Fever Therapy Technique J R
EWALT, E H PARSONS, S L WAR-
REN and S L OSBORNE *Rev* 255
- Fibrillation, Paroxysmal Auricular — in
Association with Hiatus Hernia W
D STUBENBORD *Case Rep* 406
- Flight, Medical Aspects of High Alti-
tude — D N W GRANT 1006
- Formulary and Handbook of The Johns
Hopkins Hospital J C KRAVITZ,
JR, Editor *Rev* 255
- G**ASTRIC pH, A Method for the
Continuous Recording of — in
Situ IV Further Evaluation of the
Efficacy of Antacids in Vitro and in
the Human Being N E ROSSETT
and J FLENER 193
- Gastrointestinal Disturbances of Neuro-
psychiatric Origin, The Treatment of
Functional — J C YASKIN 949
- Geriatric Medicine, Pertinent Problems
of — E J STIEGLITZ 89
- Germanic Codes, Some Probative As-
pects of the Early —, Carolina and
Bambergensis S POLSKY and S
BERESFORD 841
- E**LECTROENCEPHALOGRAPHY,
The Present Status of Clinical —
F A GIBBS 1012

- Glycosuria, Hyperglycemia and — as Means of Controlling Protamine Zinc Insulin Administration in Diabetes *Edit* 112
- Gout, Successful Treatment of — E C BARTELS 21
- Guanidine, Indole and Histamine Prophylactic and Therapeutic Detoxication —. G J MARTIN, E H RENNEBAUM and M R THOMPSON 57
- Gynecologic Surgery M A GOLDBERGER *Rev* 870
- Gynecology, Essentials of —. W R COOKE. *Rev* 1023
- H** EART Disease, The Fraudulent Use of Digitalis to Simulate — O. F HEDLEY 154
- Heart, Myxedema — A Pathological and Therapeutic Study J S LA DUE 332
- Heparin, Experimental Studies on — and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs D. I MACHT 772
- Hepatosplenography, Ten Years' Experience with Thorotrast — W M YATER and F O COE 350
- Histamine, Guanidine, Indole and — Prophylactic and Therapeutic Detoxication —. G J MARTIN, E H RENNEBAUM and M R THOMPSON 57
- Histoplasmosis, Laryngeal and Systemic — (Darling) P A. VAN PERNIS, M E. BENSON and P H HOLINGER *Case Rep* 384
- Human Plasma, Possible Substitutes for — *Edit* 251
- Hyperglycemia and Glycosuria as Means of Controlling Protamine Zinc Insulin Administration in Diabetes *Edit* 112
- Hypertension, A Progress Report of Investigations Concerned with the Experimental Treatment of — with Kidney Extracts I H PAGE, O M HELMER, K G KOHLSTADT, G F KEMPF, A C CORCORAN and R D TAYLOR. 29
- Hypoglycemic Symptoms, A Comparison of the Metabolic Effects of Isocaloric Meals of Varying Composition with Special Reference to the Prevention of Postprandial — G W THORN, J T QUINBY and M CLINTON, JR 913
- I** LEOSTOMY for Chronic Ulcerative Colitis (End Results and Complications in 185 Cases) J A BARGEN, W W LINDAHL, F S ASHBURN and J DEJ PEMBERTON 43
- Immunity in Mumps, Observations on — J F ENDERS 1015
- Indole and Histamine, Guanidine, — Prophylactic and Therapeutic Detoxication. — G J MARTIN, E H RENNEBAUM and M R THOMPSON 57
- Infant Nutrition W MCK MARRIOTT *Rev* 1023
- Insulin Content, Approximate — of Extraneous Mixtures of Insulin and Protamine Zinc Insulin F B PECK 177
- Intoxication, Legal-Medical Aspects of Blood Tests to Determine — M LADD and R B GIBSON 564
- K** ERATOCONJUNCTIVITIS, Epidemic — *Edit* 866
- Kidney Extracts, A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with — I H. PAGE, O M HELMER, K G KOHLSTADT, G F KEMPF, A C CORCORAN and R D. TAYLOR 29
- Kidneys, Acute Nephritis and the Effect of Sulfonamides on the — F D MURPHY and W D WOOD 999
- Kidneys and Brain, Severe Injury to — Following Sulfathiazole Administration High Serum Sodium and Chloride Levels and Persistent Cerebral Damage J A LUETSCHER, JR and S S BLACKMAN, JR 741
- L** ARYNGEAL and Systemic Histoplasmosis (Darling) P A. VAN PERNIS, M E BENSON and P. H. HOLINGER *Case Rep* 381
- Law and Medicine, Scientific Proof and Relations of — H W SMITH 450
- Legal-Medical Aspects of Blood Tests to Determine Intoxication M LADD and R B GIBSON 561
- Leukemia The Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy F H BRITNELL 757
- Liver Disease, Vitamin Deficiency and — *Edit* 110

Liver Extracts, Allergy to Injectable —, Clinical and Immunological Observations S M FEINBERG, H L ALT and R H YOUNG	311
Lung, Carcinoma of the —, A Review of 31 Proved Cases at the Philadelphia Naval Hospital F FTTLR	978
Lymphocytosis, Acute Thrombocytopenic Purpura Hemorrhagica with — M TAGER and K A KLINGHOFFER <i>Case Rep</i>	96
M EDICAL Aspects of High Altitude Flight D N W GRANT	1006
Medico-Legal Problems, Circulatory Deficiency in the Extremities in Relation to — Arteriosclerotic Deficiency (Including Diabetes), Thromboangitis Obliterans, or Buerger's Disease J HOMANS	518
Menière's Syndrome and Migraine Observations on a Common Causal Relationship M ATKINSON	797
Meningitis, The Relation of the Carrier to Epidemic — J H MUELLER	974
Metabolic Effects of Isocaloric Meals of Varying Composition, A Comparison of the — with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms G W THORN, J T QUINBY and M CLINTON, JR	913
Military Neuropsychiatry in the Present War C H PARSONS	935
Mumps, Observations on Immunity in — J F ENDERS	1015
Myxedema Heart A Pathological and Therapeutic Study J S LA DUE	332
N AVY, Peptic Ulcer in the United States — V W LOGAN and P W BRANSFORD	929
Navy, The Problems of the Internist in the — R E DUNCAN	920
Nephritis, Acute — and the Effect of Sulfonamides on the Kidneys F D MURPHY and W D WOOD	999
Neuropsychiatric Origin, The Treatment of Functional Gastrointestinal Disturbances of — J C YASKIN	949
Neuropsychiatry, Military — in the Present War E H PARSONS	935
Nutrition, Infant — W MCK MARRIOTT <i>Rev</i>	1023

OBITUARIES

Allen, Theophilus Powell	885
Bonney, Sherman Grant	266
Brown, William Byrnes	716
Byrnes, Ralph L	886
Casparis, Horton Ryan	267
Dennison, Archibald S	1038
Elward, Joseph F	887
Freeman, Elmer Burkitt	431
Gundrum, Frederick Fretageot	267
Jackson, Algernon Brashear	143
Kruse, Fred Herman	716
Layton, Oliver M	715
Milliken, Herbert Eldridge	717
Porter, Ernest Boring	718
Ricen, Leo	430
Ripps, Maurice L	268
Rowland, Peter Whitman	715
Settle, George Meade	430
Stewart, Harry Myrrel	888
Stofer, John William	1038
Unger, Isedor Mack	888
Waddell, Charles Walter	885
Watkins, F B	1037
Wilmer, Harry Bond	432
Work, Hubert	269
P ANCREATIC Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease C KLEIN, G SALAND and H ZURROW	214
Parathyroidectomy, Calcinosi and Scleroderma with — C S BYRON and S MICHALOVER <i>Case Rep</i>	225
Paroxysmal Auricular Fibrillation in Association with Hiatus Hernia W D STUBENBORD <i>Case Rep</i>	406
Pediatrics, Advances in — A G DESANCTIS, Editor <i>Rev</i>	704
Peptic Ulcer in the United States Navy V W LOGAN and P W BRANSFORD	929
Phenobarbital, Exfoliative Dermatitis Due to — S W BAREFOOT and J L CALLAWAY <i>Case Rep</i>	105
Physical Biochemistry, Introduction to — J M JOELIN <i>Rev</i>	116
Plasma, Possible Substitutes for Human — <i>Edit</i>	251
Pneumococcus, Type VIII — Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers A W FRISCH, A E PRICE and G B MYERS	271

- Pneumonia, Newer Knowledge Concerning the Inception of — and Its Bearing on Prevention O H ROBERTSON 1
- Pneumonia, Sulfur Dioxide Chemical —, Report of a Case with Recovery Following Accidental Explosion of a Refrigerator Unit H L GOLDBURGH and B A GOULEY *Case Rep* 237
- Privileged Communications Is Justice Served or Obstructed by Closing the Doctor's Mouth on the Witness Stand? Z CHAFFEE, JR 606
- Problems of Fluid Balance in the Traumatized Patient J E RHOADS 988
- Problems of Proof in Claims for Recovery for Dermatitis L SCHWARTZ 500
- Problems of the Internist in the Navy, The — R E DUNCAN 920
- Prostatic Hypertrophy, Circulatory Disturbances in — M MALLORY, F MATHERS, L M ORR II and P R KUNDERT 835
- Protamine Zinc Insulin Administration in Diabetes, Hyperglycemia and Glycosuria as Means of Controlling — *Edit* 112
- Protamine Zinc Insulin, Approximate Insulin Content of Extemporaneous Mixtures of Insulin and — F B PICK 177
- Protozoan Diseases, Laboratory Diagnosis of — C F CRAIG *Rev* 704
- Psychoneuroses in War Time L H ZIEGLER 941
- Psychoses, A Review of the Drastic Shock Therapies in the Treatment of the — F G EBAUGH 279
- Psychoses, Traumatic — F G EBAUGH and H W BROSN 666
- Psychosomatic Medicine, The Leaven of — E A STRICKER 736
- Pulmonary Thrombosis, Abdominal Pain in — W S MIDDLETON 345
- R**ENAL Function, Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on — J B KIRSNLR and W L PALMER *Case Rep* 100
- Roentgen-Ray Medical Facts That Can or Cannot Be Proved by —, Historical Review and Present Possibilities S W. DONALDSON 535
- S**CIENTIFIC Proof and Relations of Law and Medicine H W SMITH 450
- Scleroderma, Calcinosis and — with Parathyroidectomy C S BYRON and S MICHALOVER *Case Rep* 225
- Senescence, Factors Which May Influence — N S DAVIS III 81
- Shock Therapies, A Review of the Drastic — in the Treatment of the Psychoses F G EBAUGH 279
- Sodium Bicarbonate, Studies on the Effect of Massive Quantities of — on the Acid Base Equilibrium and on Renal Function J B KIRSNLR and W L PALMER *Case Rep* 100
- Spa Therapy, An Experience in — New Trends in the Treatment of Chronic Disease — W. S. MCCLELLAN 825
- Sphygmotonograph, A Recording — A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man K LANGE 367
- Sterilization, Certain Medical and Legal Phases of Eugenic — A MYERSON 580
- Sterilization, Compulsory Vaccination and — Constitutional Aspects T R POWELL 637
- Stomach, Cancer of the — with Special Reference to Early Diagnosis I W HELD and I BUSCH 719
- Subacute Bacterial Endarteritis Complicating Patent Ductus Arteriosus Case Report with Recovery Following Sulfapyridine-Heparin Therapy W A. WINN, C L HUGHES and J M SANDERS *Case Rep* 242
- Sugar Alcohols XXIV The Metabolism of Sorbitol in Diabetes F W ELLIS and J C KRANTZ, JR 792
- Sulfadiazine Resistance, Development of —, Transmission by Cross Infection, and Persistence in Carriers Type VIII Pneumococcus — A W FRISCH, A E PRIOR and G B MYERS 271
- Sulfapyridine-Heparin Therapy, Case Report with Recovery Following — Subacute Bacterial Endarteritis Complicating Patent Ductus Arteriosus — W A WINN, C L HUGHES and J M SANDERS *Case Rep* 212
- Sulfathiazole Administration, Severe Injury to Kidneys and Brain Follow-

- ing — High Serum Sodium and Chloride Levels and Persistent Cerebral Damage J A LUETSCHER, JR and S S BLACKMAN, JR 741
- Sulfonamide Therapy of Bacterial Endocarditis, Results in 42 Cases W R GALBREATH and E HULI 201
- Sulfonamides, Acute Nephritis and the Effect of — on the Kidneys F D MURPHY and W D WOOD 999
- Sulfur Dioxide Chemical Pneumonia, Report of a Case with Recovery Following Accidental Explosion of a Refrigerator Unit H L GOLDBURGH and B A GOULEY *Case Rep* 237
- Surgery, Gynecologic — M A GOLDBERGER *Rev* 870
- Synopsis of Ano-Rectal Diseases L J HIRSCHMAN *Rev* 1023
- Syphilis of the Stomach W L PALMER, R SCHINDLER, F E TEMPLETON and E M HUMPHREYS *Case Rep* 393
- T**AXES, The Doctor's Federal — E N GRISWOLD 647
- Thorotrast Hepatosplenography, Ten Years' Experience with — W M YATER and F O COL 350
- Thromboangitis Obliterans in Young Draftees, Recognition of Incipient — W E JAHSMAN and R H DURHAM 164
- Thrombocytopenic Purpura Hemorrhagica, Acute — with Lymphocytosis M TAGER and K A KLINGHOFFER *Case Rep* 96
- Thrombosis, Abdominal Pain in Pulmonary — W S MIDDLETON 345
- Tort Liability of Hospitals A W SCOTT 630
- Traumatic Disease, Clinical Approach to Alleged — L BRAHDY and S KAHN 491
- Traumatic Psychoses F G EBAUGH and H W BROSIN 666
- Traumatic Wounds of Human Tissues, The Relation of the Crush Syndrome to That of Burns and Other Types of — W E LEE 991
- Traumatized Patient, Problems of Fluid Balance in the — J E RHOADS 988
- Tularemia A Report of Four Cases with Unusual Contacts J H SHAFFER 72
- Tuning Fork Auscultation A Test for Abdominal Adhesions B B V LYON 297
- Type VIII Pneumococcus Development of Sulfadiazine Resistance, Transmission by Cross Infection, and Persistence in Carriers A W FRISCH, A E PRICE and G B MYERS 271
- V**ACCINATION and Sterilization, Compulsory — Constitutional Aspects T R POWELL 637
- Vascular Disease, Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral — C KLEIN, G SALAND and H ZURROW 214
- Vitamin Deficiencies, Postoperative Precipitation of — M ELLENBERG, H DOLGER and H POLLACK *Case Rep* 110
- Vitamin Deficiency and Liver Disease *Edit* 410
- W**AR, Military Neuropsychiatry in the Present — E H PARSONS 935
- War, The College and the — E L BORTZ *Edit* 1020
- War Time, Cardiac Problems in — P D WHITE 323
- War Time, Psychoneuroses in — L H ZIEGLER 941

gestion or persuasion Psychoanalysis is said to be helpful They border on depression or melancholia, and may be responsive to sleep treatment, insulin to the point of inducing sleep, and even to electric shock therapy Because of the disposition to have rapid pulse and perspire freely, the treatment must have especially close supervision Many of these disorders are erroneously mistaken for toxic goiter Mild sedation is desirable throughout the 24 hours to enable the patient to feel more secure These patients are often suicidal and definite precautions should be taken to prevent it. They constitute in their variety by far the larger part of the psychoneuroses developing on the battle field

5 *Hypochondriasis—Hypochondriacal States* These disorders originally referred to the region under the costal cartilages (hypo-kondria), because other parts of the body may be implicated, the term is really another misnomer To such patients the body rarely feels comfortable The abdomen is distressing, the heart may feel heavy, the lungs may be suspected, the genitals may cause discomfort Bizarre notions sometimes exist, such as "the blood drying up, the stomach rotting, the lungs filling up, the liver clogging, the heart losing its power, the face becoming distorted" Such patients declare that they would be well except for such varied and unpleasant feelings, and they go from one physician to another seeking relief Personal disintegration takes the form of *body distress and discomfort*—not on a mimicry basis—but with *delusions about their cause* They resemble paranoia in that they project their distress to the body, however, instead of to the environment These patients are not weak and struggle to carry on Hypochondriasis differs from invalidism in that these patients are more capable of working, part of the time at least These disorders are doubtless closely related to some of the more overt psychoses, and are known for their chronicity and unresponsiveness to treatment Fortunately they are rare

6. *Traumatic, Post-traumatic, Post-concussion Neurosis* It has long been known that a disabling syndrome may occur following severe trauma, or shock It may take many forms, and change in mood, loss of energy, uncomfortable and distressing feelings are common However, the mere fact that it does not occur in all cases of severe trauma, but merely in a few, gives strong proof to the theory that only certain persons are predisposed Electroshock and metrazol shock have taught us many things Chief of these is that shock drives the patient from one emotional state into another This leads us to suspect that severe trauma or concussion, or the effect of violent blast, may dislocate the emotional integrity of otherwise well, but predisposed persons, to make them ill This is really *modern shock treatment in reverse* Such disorders heretofore called post-traumatic or post-concussion neuroses are usually affective disorders A small percentage may fall into the group of neuroses previously described, especially in view of the fact that the possibility of compensation may add impetus to certain

forms of mimicry and defensiveness. The physiological and anatomical effects which may result from violent trauma and blast are not adequately understood and constitute a fertile field for research. For these reasons, post-traumatic or post-concussion neurosis may be misnomers which, as we have seen, have been so prevalent in the nomenclature of psychoneuroses.

Treatment of the psychoneuroses must be individual, but should be planned so that we do not expect more of the patient than he can honestly deliver. For those whose adaptability has become strained or bankrupt, let us provide therapeutic facilities of all types, hopefully, and for a reasonable time. Psychoanalysis takes too long for more than a few patients, although some shorter modifications of it may be useful. Insulin may be employed to induce sleep, or a better state of nutrition. Electric shock may be very helpful on occasion. Mild sedation, graduated exercise, physiotherapy, occupational therapy, recreational activities, psychotherapy—teaching the patient to live within his capacities, to divorce himself from inflated ambitions—all of these will help the psychoneurotic to utilize his assets and to feel his defects and disabilities less painfully. Treatment, except in the hands of the experienced, causes these patients to seek help far and wide, in and out of the medical profession.

The word "psychoneurosis" has many meanings to different people. It is not a condemnatory term, but should conjure up a descriptive picture that of a person disabled in any one of the several quite specific ways I have previously sketched. It is not a negative entity, it is really a very positive one. It is rarely pure combinations exist, one of the chief being depression, with neurotic tendencies. Whether the disorder is a mild psychosis or a neurosis is often the source of fruitless academic argument. One thing seems certain, such patients appeal to the internists and surgeons repeatedly for help before they finally come to the psychiatrist. They may accumulate a collection of surgical scars in their quest for relief. All too frequently they are treated as time-consuming intruders because of the paucity of physical findings. The psychoneurotic is, of course, subject to all the diseases of the body that can attack anyone else, and may even become psychotic.

Psychoneurotics, except for the severer but rarer forms encountered on the battlefield, are not completely disabled. They carry on by fits and starts, seasonably and sporadically, often compensating for energy defects by engaging in intellectual pursuits. I know one whose specialized judgment in the financial world enabled him, in a brief period, to make a large sum of money while in bed with his disability. The psychoneurotic is sensitive and often makes up for quantity by the quality of his work. He is included among the artists and the aesthetic. In spite of his disabilities, we are indebted to him for contributing to a more refined world in which to live, and he needs what help we can bring to him.

War does not cause psychoneurosis, except as the predisposed are broken down by it. War requires strenuous, continuous effort, often in the presence of unspeakable horrors. It is a race for the strong and the tough and